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Summer Session, 1964

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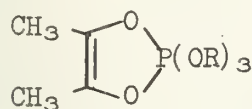
THE REACTION OF α -DIKETONES WITH TRIALKYL PHOSPHITES

Reported by Earl G. Alley

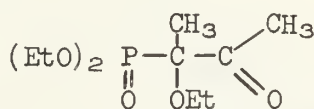
June 24, 1964

Introduction.--Interest in the reactions of esters of phosphorous acid with carbonyl compounds has arisen mainly because the products undergo Arbuzov type rearrangements (1). In addition to the reactions of trialkyl phosphites with α -dicarbonyl compounds, which are the subject of this review, the reactions of trialkyl phosphites with alkyl halides, alcohols, aldehydes, ketones and anhydrides have been studied (1). The reactions of trialkyl phosphites with p-quinones give products the structures of which are the subject of controversy (2,3,4).

Reactions of α -diketones with Trialkyl Phosphites (1:1 Adducts).--The first report of a reaction between a trialkyl phosphite and an α -diketone was by Kukhtin (5) in 1958. He found that the reaction of triethyl phosphite with biacetyl at room temperature in ether for several hours, gave a product which was assigned structure I, (R=Et). The refractive index and elemental analysis (phosphorus) were given for this compound, but no evidence was cited in support of its structure. In later work (6)



I

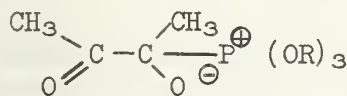


II

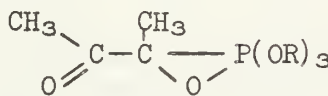
another product of the reaction was observed and assigned structure II. Upon heating or standing in contact with air I could be converted to II (6). Heating I, (R=Et), in an inert atmosphere causes it to revert to

starting materials (7). The structure of II was established from its infrared spectrum which exhibited bands at 1721 cm^{-1} (C=O), 1274 cm^{-1} (P=O), and 1050 cm^{-1} (P-O-C) (8).

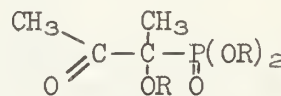
The preparation of 1:1 adducts from α -diketones and alkyl phosphites is general and many examples are now known (9,10,11,12). Kukhtin (6,7,13,14), and Ramirez (10) have obtained evidence which establishes the structure of the trialkyl phosphite-biacetyl 1:1 adduct as I, and eliminates III, IV, V, VI, and VII as possible structures.



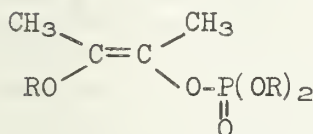
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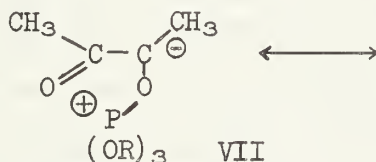
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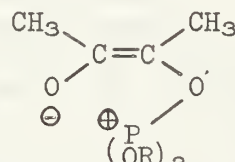
V



VI



VII



Structures III, IV and V cannot be correct because the adduct does not exhibit in its infrared spectrum the absorption typical of a carbonyl group, and the ultraviolet spectrum shows only end absorption (6). However, the infrared spectrum does show weak absorption at 1730 cm^{-1} and the Raman spectrum shows strong absorption at 1740 cm^{-1} (6,10); these facts are in accord with the assignment of symmetrically substituted carbon-carbon double bond stretching frequency to these bands.

Phosphate and phosphonate esters generally exhibit strong absorption between 1250 cm^{-1} - 1350 cm^{-1} (8). The 1:1 biacetyl-trimethyl phosphite adduct exhibits infrared absorption at 1250 cm^{-1} (medium), 1294 cm^{-1} (weak), and 1393 cm^{-1} (weak) (10). These bands do not have the intensity associated with the P=O stretching vibration. The P-O-C bonds of methyl phosphate absorb strongly at 1045 cm^{-1} (8). The strongest bands in the infrared of the adduct in this region are found at 1090 cm^{-1} and 1075 cm^{-1} (10). Thus the structure VI which has phosphate linkage is eliminated as the structure of the 1:1 adduct.

The structures that remain to be considered are I and dipolar form such as VII. Structure I is favored over structure VII because of the following data. The adduct does not behave as a strongly polar compound; it can be distilled, is very soluble in

non-polar solvents (10,13), and has a dipole moment of 2.5 D (6). The ^{31}P n.m.r. spectra of all the α -diketone-trialkyl phosphite adducts studied falls in the range from +46 to +62 p.p.m. relative to high field of 85% H_3PO_4 (Table I). A list of other ^{31}P chemical shifts for comparison appears in Table II. The effect of adding one more oxygen to a trialkyl phosphite causes a large change in the chemical shift

TABLE I

(10)

α -Diketone	R in $\text{P}(\text{OR})_3$	P.P.M. (Relative to 85% H_3PO_4)
Phenanthrenequinone	Methyl	+49
Phenanthrenequinone	Phenyl	+58
Benzil	Methyl	+53
Benzil	Isopropyl	+54
Benzil	Phenyl	+62
Biacetyl	Methyl	+53
Biacetyl	Isopropyl	+51
2,3-Pentanedione	Methyl	+46

TABLE II

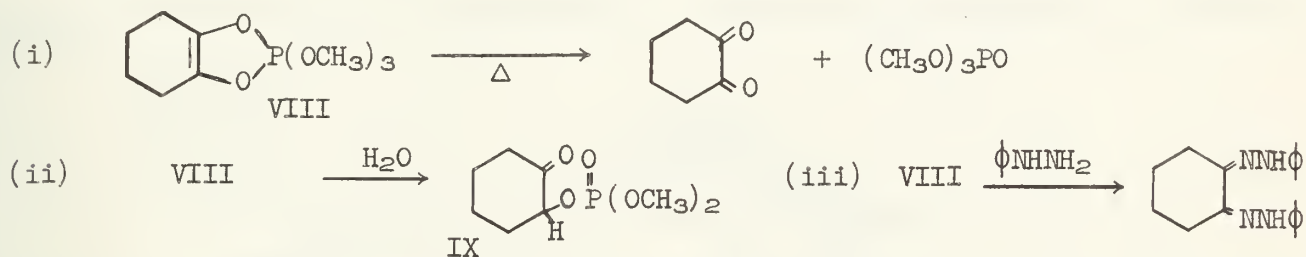
(15)

Compound	P.P.M. (Relative to 85% H_3PO_4)
$(\text{O})_3\text{PO}$	+17
$(\text{O})_3\text{P}$	-126
$(\text{EtO})_3\text{PO}$	+ 1
$(\text{EtO})_3\text{P}$	-137
Cl_3P	-219
Cl_5P	+78
Cl_3PO	- 2
PCl_5 (crystalline)	-91, +281 (16)

towards high field. No data are available on tetraalkoxy phosphonium salts, which would be good models for VII. According to Ramirez (10), it is not likely that these compounds would have a large positive chemical shift, because the oxygen atom of the fourth alkoxy group would be expected to shield the phosphorus less in the tetraalkoxy phosphonium salts than the fourth oxygen does in the phosphate esters. Furthermore Ramirez points out (10), that the covalent bond between oxygen and phosphorus in structure I would be more effective in shielding magnetically the phosphorus atom than would the approach of the two ends of the dipolar form. The principles upon which these conclusions were drawn are of dubious validity. It is likely that the hybridization and bond angles at phosphorus are the dominating influences in the observed changes in chemical shift rather than simple shielding or deshielding by oxygen. Ramirez and coworkers (10) have attempted to calculate the expected chemical shift of $\text{P}(\text{OEt})_5$ and $\oplus\text{P}(\text{OEt})_4$ by correlation with the values of known compounds (Table II). They have noted that the values of the percent changes in the chemical shifts of $(\text{EtO})_3\text{P}$ to $(\text{EtO})_3\text{PO}$ and Cl_3P to Cl_3PO are almost identical. The percent change in the chemical shift of PCl_3 to PCl_5 was calculated. This value was then used to calculate the chemical shift for $\text{P}(\text{OEt})_5$ from $\text{P}(\text{OEt})_3$. The percent change in chemical shift from PCl_3 to $\oplus\text{PCl}_4$ (using the low field resonance peak of crystalline PCl_5 for the chemical shift of $\oplus\text{PCl}_4$) was calculated. This percent change was then used to calculate a chemical shift for $\oplus\text{P}(\text{OEt})_4$ from $\text{P}(\text{OEt})_3$. The results of these calculations are +49 for $\text{P}(\text{OEt})_5$ and -61 for $\oplus\text{P}(\text{OEt})_4$. The former value is very close to that observed for the 1:1 adducts. It should be pointed out that these calculations probably have little validity because the values obtained are dependent upon the reference chosen to calibrate the spectra.

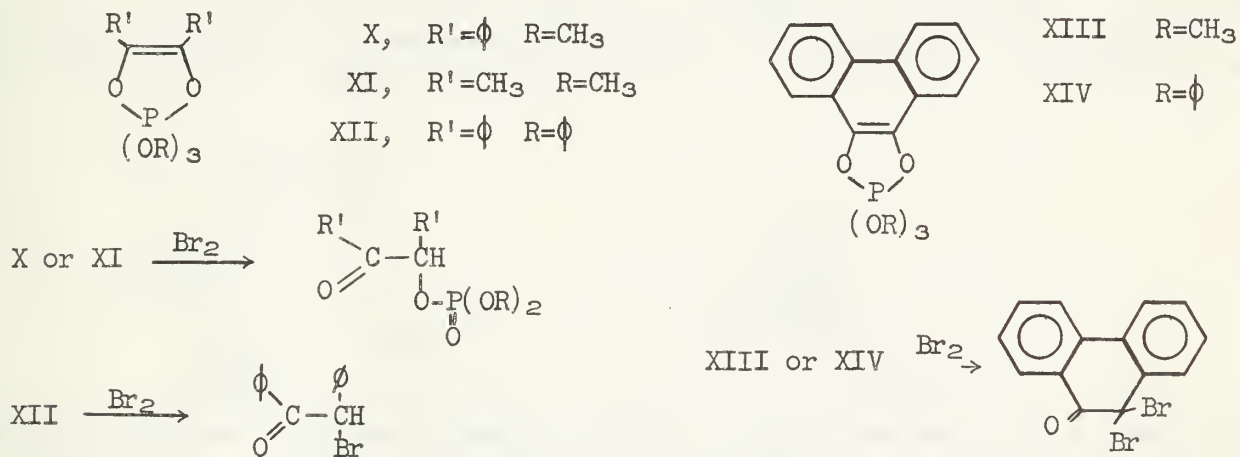
The ^1H n.m.r. spectrum (6,10) of the 1:1 biacetyl-trimethyl phosphite adduct revealed a doublet (9H) at $\tau 6.56$, ($J_{\text{HP}}=13$ c.p.s.) and a singlet (6H) at $\tau 8.25$. The methoxyl protons ($\tau 6.56$) are split by ^{31}P and are either equivalent or indistinguishable. The peak at $\tau 8.25$ is a single, unsplit peak which indicates that these methyl groups occupy similar positions. These data favor the cyclic covalent structure I.

The reactions of the 1:1 adducts have been studied by several groups of workers. Kukhtin and coworkers (11) found that heating the 1:1 adducts in methanol converts them to the original diketone and trialkyl phosphate. These results probably arise from reversion to starting materials followed by oxidation of the trialkyl phosphite formed to trialkyl phosphate by air. Ramirez and coworkers obtained somewhat similar results when they sealed the 1:1 adducts under oxygen for five days. The products were 10-30% of the anhydride corresponding to the original diketone, about 60% of the diketone and about 90% of the trialkyl phosphate (17). Kukhtin and coworkers (11) also observed the following reactions (i, ii, iii) of the 1:1 adduct of cyclohexane-1,2-dione and trimethyl phosphite. The ketophosphate IX could also be obtained from VIII



by standing in air for one month. No evidence was cited in support of the structures of these products. Similarly Birum and Dever reported (28) that the 1:1 biacetyl-trialkyl phosphite adducts yield upon reaction with water dialkyl-1-methyl-2-oxopropyl phosphates. Ramirez and coworkers (18) found results similar to (ii) and 1:1 adducts are treated with anhydrous hydrogen chloride.

The reactions of various 1:1 adducts with bromine are summarized below: (17)

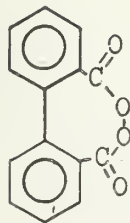


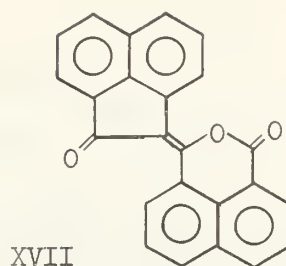
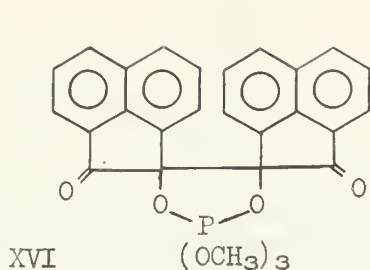
No evidence was given in support of the structures of the products of these reactions. The reaction of XIII with ozone has been investigated (19) and was shown to yield diphenoyl peroxide, XV. Similarly the 1:1 adduct from benzil and trimethyl phosphite yields benzoyl peroxide (20).

Reaction of 1:1 Adducts with α -Diketones. (2:1 Adducts).--

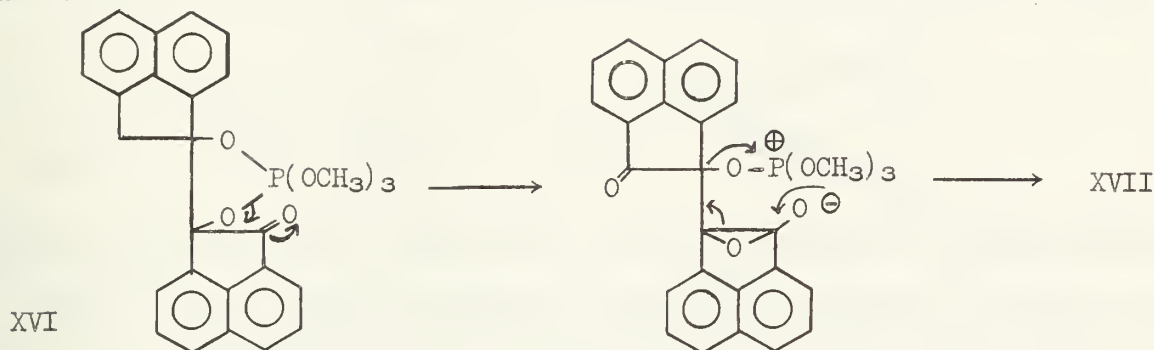
Ramirez and his coworkers have observed (21-26), that the 1:1 adducts are capable of reacting with another mole of α -diketone to form 2:1 adducts. The first example of a 2:1 adduct they reported (21) was the adduct of acenaphthenequinone and trimethyl phosphite, to which structure XVI was assigned. The only evidence cited in support of structure XVI was an elemental analysis and that its infrared spectrum had bands at 1740 cm⁻¹ (carbonyl) and between 1050 and 1100 cm⁻¹ characteristic of P-O-C- vibrations (8). When refluxed with methanol, XVI yielded a product whose structure was postulated to be XVII, on the basis of its infrared spectrum, its analysis, and its reaction with 1N NaOH to form 1,8-naphthoic acid and acenaphthenone. XVII has two absorption bands in the

XV

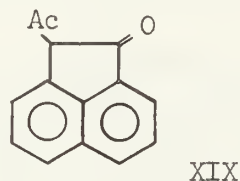
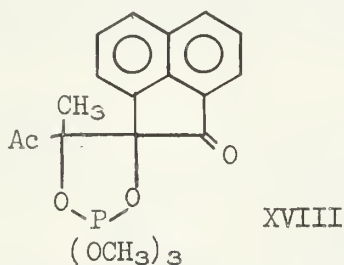




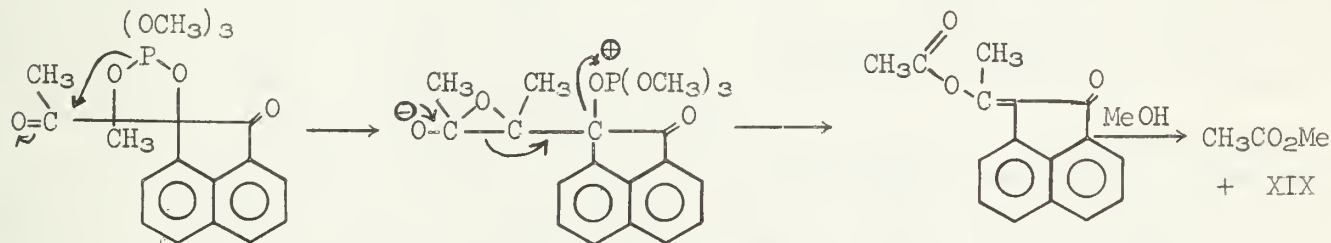
carbonyl region at 1667 cm^{-1} and 1695 cm^{-1} . A possible mechanism for the formation of XVII is:



A mixed biacetyl-acenaphthenequinone adduct has also been prepared (22). The mixed adduct was synthesized by the reaction of the 1:1 biacetyl-trimethyl phosphite adduct with acenaphthenequinone. The mixed adduct was assigned structure XVIII. The adduct showed strong absorption in the carbonyl region at 1707 and 1719 cm^{-1} , along with bands at 1085 - 1075 cm^{-1} associated with the P-O-C vibrations (8). Adduct XVIII when

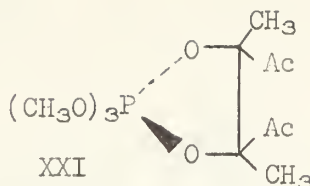
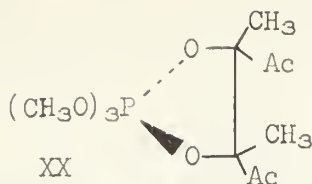


treated with methanol yielded trimethyl phosphate, methyl acetate, and 1-acetyl-2-acenaphthenone XIX. The mechanism for this rearrangement is probably similar to that

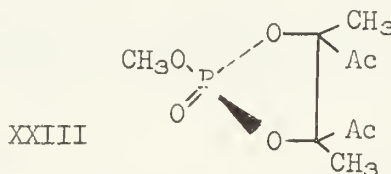
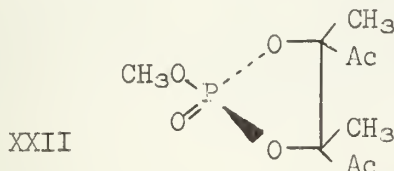


postulated (21) for the rearrangement of the 2:1 acenaphthenequinone-trimethyl phosphite adduct XVI. The β -diketone XIX was cleaved by dilute alkali to acenaphthenequinone.

The 2:1 biacetyl trimethyl phosphite adduct has been prepared (22,25,26), by Ramirez *et al.* This adduct was produced as a mixture of diastereomers XX and XXI. This mixture was separated into XX and a 50:50 mixture of XX and XXI. The ^{31}P n.m.r. spectra of the mixture and of XX showed absorption at ca. +50 p.p.m. Both XX and the mixture exhibited absorption in their infrared spectra typical of carbonyl stretching vibrations (ca. 1715 cm^{-1}) and of P-O-C vibrations (strong bands from 1080 - 1110 cm^{-1}).

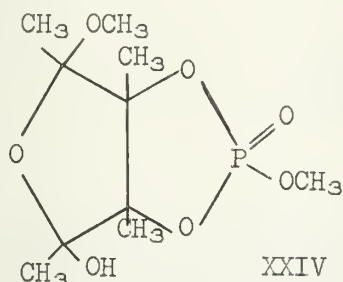


Their ^1H n.m.r. spectra showed doublets at ca. $\tau 6.50$ ($J_{\text{HP}}=13$ c.p.s.), singlets at ca. $\tau 7.70$ and $\tau 8.70$. In the mixture the sets of peaks for both XX and XXI can be seen. The relative peak areas were those expected for the assigned structures. When XX was treated with water in aprotic solvents a substance, assigned structure XXII was obtained. If the mixture of XX and XXI is subjected to these same hydrolytic conditions



a mixture of diastereomers results which could be separated into meso XXII and racemic XXIII.

The ^1H n.m.r. spectrum of freshly prepared XXII exhibits a doublet at $\tau 6.07$ (3H) ($J_{\text{HP}}=12$ c.p.s.) and singlets at $\tau 7.65$ (6H) and $\tau 8.42$ (6H). If the sample of XXII is allowed to stand for a few days a new set of peaks, a doublet at $\tau 6.15$ ($J_{\text{HP}}=12$ c.p.s.) and singlets at $\tau 7.70$ and $\tau 8.35$, appears in addition to those in the spectrum of XXII. The new set of peaks has the same ratios of peak areas as those in the spectrum of XXII. The ^1H n.m.r. spectrum of XXIII shows a doublet at $\tau 6.00$ ($J_{\text{HP}}=12$ c.p.s.) and singlets at $\tau 7.60$, $\tau 7.65$, $\tau 8.43$ and $\tau 8.53$ with ratios 1:1:1:1. These spectra are consistent with the assignment of the meso configuration to XXII and the racemic structure to XXIII. The appearance of the new set of lines in the spectrum of XXII which does not occur with XXIII can be explained in terms of an epimerization at phosphorus. Only in the case of XXII does such a process yield something other than the original isomer.



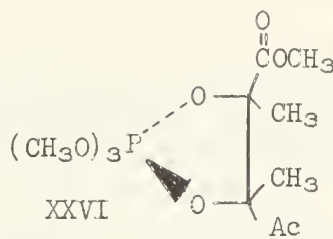
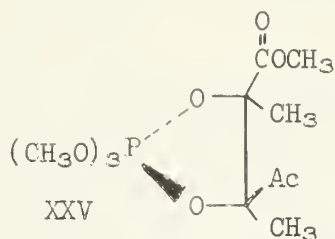
The structural assignments XXII and XXIII are supported by chemical data (26). When XX is allowed to react for twenty hours with water, the methanol formed in the production of XXII reacts further with XXII to form a furanose cyclic phosphate XXIV. The ready formation of this hemiketal suggests (26) that the acetyl groups in XX must be cis to each other. The structure XXIV was supported by its infrared spectrum with bands at 3740 cm^{-1} (OH), 1280 cm^{-1} (cyclic P=O), and a strong band at 1050 cm^{-1} (methyl phosphate), and its ^1H n.m.r. spectrum which had signals at $\tau 5.77$ (OH), a doublet at $\tau 6.15$ ($J_{\text{HP}}=12$ c.p.s.), (POCH₃) and singlets at $\tau 6.65$ (COCH₃), $\tau 8.50$, $\tau 8.55$ (double intensity), and $\tau 8.58$. Co-distillation of XXIV with benzene caused loss of methanol and reversion to XXII.

The formation of the cyclic phosphates XXII and XXIII from the corresponding 2:1 adducts provides further chemical evidence for the structures assigned to these adducts. If XX and XXI had open dipolar structures (cf. VII), one would expect (26), that hydrolysis would yield an open chain phosphate ester, since it appears most unlikely that open chain phosphate esters would cyclize under the conditions of the reaction.

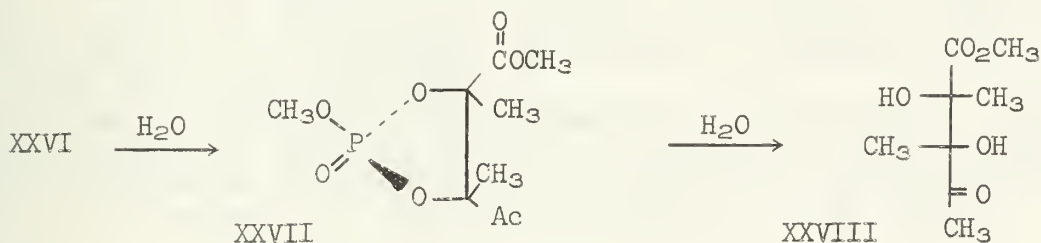
Hydrolysis of the adducts XXII and XXIII with water in refluxing benzene yielded 3,4-dimethyl-3,4-dihydroxy-2,5-hexanedione (26). Only the meso compound is formed from XXII. Racemic diketol with small amounts of the meso diketol resulted from hydrolysis of XXIII. Therefore some epimerization must occur in the latter case. The structures of the diketols were established with infrared and n.m.r. spectra.

The reaction of the 1:1 biacetyl-trimethylphosphite adduct with methyl pyruvate has been studied (23,24). The products were postulated to be the pair of diastereomers

XXV and XXVI. Only compound XXVI was isolated. Its structure has been established from its infrared spectrum which showed bands at 1735 cm^{-1} (ester $\text{C}=\text{O}$), 1715 cm^{-1}

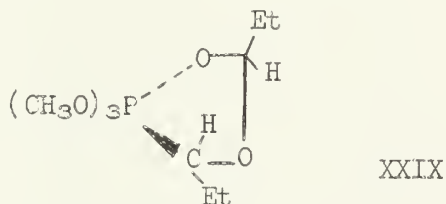


(ketone $\text{C}=\text{O}$), and $1075\text{--}1085\text{ cm}^{-1}$ (P--O--C), and its ^1H n.m.r. with singlet $\tau 6.35$, doublet $\tau 6.52$ ($J_{\text{HP}}=13\text{ c.p.s.}$), singlet $\tau 7.83$, singlet $\tau 8.57$ and singlet $\tau 8.76$, and by the following reactions. When hydrolyzed with water in benzene solution it gave the cyclic phosphate XXVII. This cyclic phosphate was hydrolyzed further in aqueous solution (pH 4.0-4.5) to dl-threo-methyl- $\alpha\beta$ -dimethyl- $\alpha\beta$ -dihydroxy levulinate XXVIII. This same



product could be obtained by hydrolysis of XXVI in aqueous solution. The assignments of the structures XXVII and XXVIII were made on the basis of their infrared and n.m.r. spectra.

Ramirez has also reported (27) that the reaction of 1:1 adducts with monocarbonyl compounds give compounds with structures similar to the 2:1 adducts and that the reaction of propionaldehyde with trimethyl phosphite yielded a substance which he proposed had structure XXIX.



Conclusion.—The studies of the preparation and reactions of these 1:1 and 2:1 adducts are of interest because of the rarity of compounds having phosphorus with five groups attached. The carbon-carbon condensation involved in the formation of the 2:1 adducts may be of synthetic value.

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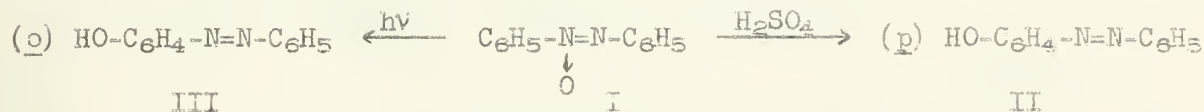
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THE MECHANISM OF THE WALLACH REARRANGEMENT

Reported by David A. Durand

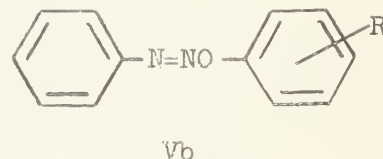
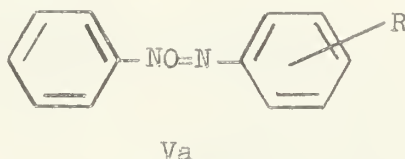
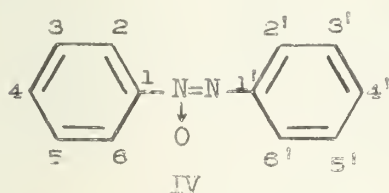
June 29, 1964

Introduction: It has been known for many years that treatment of azoxybenzene (I) with concentrated sulfuric acid results in the formation of *p*-hydroxyazobenzene (II); in contrast, the action of ultraviolet light upon I yields *o*-hydroxyazobenzene (III). These transformations, known as the Wallach rearrangement, pose an interesting



mechanistic problem for the organic chemist. Most of the early work in this field is of limited value because it involved the application of older concepts of mechanism and structure, and sophisticated experimental techniques were not available. However, the use of isotopic tracers in mechanistic studies has brought about a renewal of interest in this rearrangement. Since there is still a great deal of controversy over the mechanisms proposed, it is the purpose of this seminar to present and correlate the available data and to draw such conclusions as are warranted by these data.

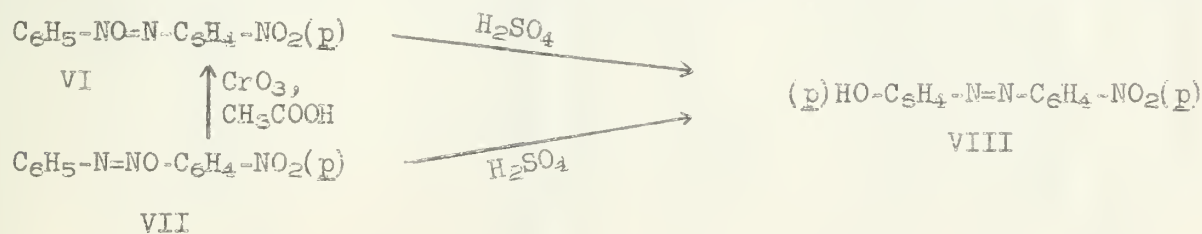
The numbering system for azoxybenzene is given below (IV). Because of the unsymmetrical nature of the azoxy group, there exist two structural isomers for every monosubstituted azoxybenzene; by convention these forms are termed " α " (Va) and " β " (Vb).



The Para-Rearrangement:

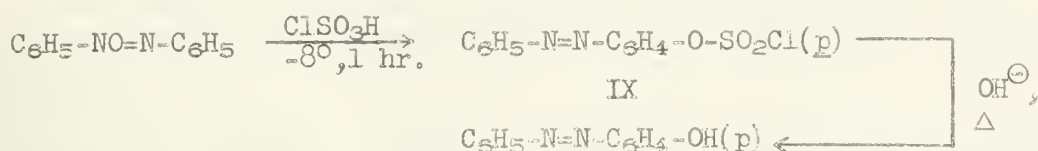
Early Work: In 1880, Wallach (1) found that azoxybenzene dissolved in concentrated sulfuric acid to form a bright red solution. Upon workup of the reaction mixture, he was able to isolate azobenzene and a red acidic material, $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}$, which was identified as *p*-hydroxyazobenzene by comparison with an authentic sample. Using steam distillation, Bamberger (2) was able to isolate a small amount of *o*-hydroxyazobenzene from the same reaction mixture. A more extensive investigation (3) revealed that treatment of azoxybenzene with sulfuric acid produced not only hydroxyazobenzene and azobenzene, but also various amines, soluble sulfonic acids, and polymers, the relative yields of which varied with the acid concentration, the ratio of reactants, and the temperature of the reaction.

Only one of the many early studies (4) of the rearrangements of substituted azoxybenzenes is of more than passing interest. From the peracetic acid oxidation of *p*-nitroazobenzene, Angeli (4c) isolated two isomeric *p*-nitroazoxybenzenes which he labelled " α " and " β ". (It should be noted that the structures of these isomers were unknown at that time, as the unsymmetrical character of the azoxy group was not established until 1933 (5). It was observed, however, that the " β " isomer readily underwent bromination whereas the " α " isomer did not. This suggests that Angeli's " α " and " β " forms had structures VI and VII respectively.) Both isomers rearranged in



sulfuric acid to p-nitro-p'-hydroxyazobenzene (VIII); moreover, the "β" form isomerized to the "α" in the presence of chromic anhydride. Angeli accounted for the formation of only one nitrohydroxyazobenzene by proposing that such an isomerization preceded the Wallach rearrangement.

Lukashevich and Kurdyumova (6) have found that azoxybenzene rearranges in cold chlorosulfonic acid to a reasonably stable chlorosulfonic ester (IX) which can be quantitatively hydrolyzed to p-hydroxyazobenzene. Although no analogous intermediate



was isolated from the rearrangement in sulfuric acid, the authors postulated that in this case a sulfuric ester was formed and immediately hydrolyzed to p-hydroxyazobenzene.

Product Studies: In 1950, Gore and Hughes (7) reinvestigated most of the previous work on the Wallach rearrangement (much of which they found to be erroneous) and reported an extensive study of the products of this reaction. On the basis of these investigations, the reaction scheme shown in Figure 1 was proposed:

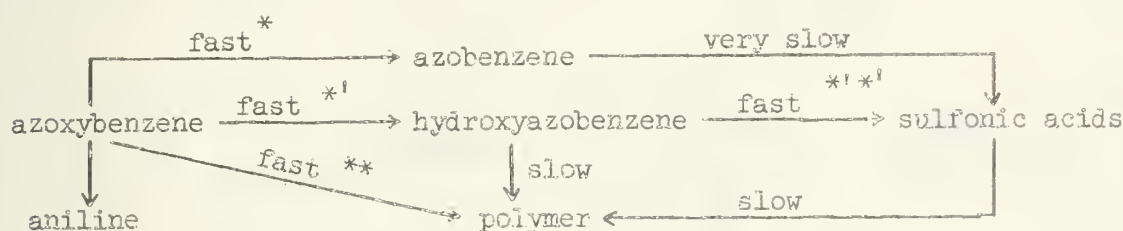


Figure 1

* faster than **

*' faster than *'*

The yield of p-hydroxyazobenzene varied widely with reaction conditions, but was highest in 83% sulfuric acid (monohydrate) at a temperature somewhat below 100°. Higher concentrations of acid and higher temperatures were found to favor the formation of the by-products. The yield of o-hydroxyazobenzene was invariably very low except in those cases in which both p-positions were substituted. The polymer was postulated to be a polyazobenzene containing free hydroxy and sulfonic acid groups. With regard to the mechanism of hydroxyazobenzene formation, the authors postulated a protonation of the azoxy group followed by the migration of hydroxy radical or ion to the p-position of the benzene ring; a more detailed treatment was not given.

The results of various recent product studies of the rearrangements of substituted azoxybenzenes are summarized in Table 1:

TABLE 1: The Wallach rearrangement of substituted azoxybenzenes

Expt.	Azoxybenzene	% H ₂ SO ₄ , Temp., Time	Hydroxyazobenzene	% Yield	Ref.
1	4-Br(α or β)	*	4-OH-4'-Br	quant.	(8)
2	4-MeO(α or β)	*	4-OH-4'-MeO	quant.	(8)
3	4-Me(α or β)	*	2-OH-4'-Me	quant.	(8)
4	3-NO ₂ (α or β)	82%, 90°, 15 min.	4-OH-3'-NO ₂	65-77	(9)
5	2,2'-diCl	98%, 90°, 1 hr.	4-OH-2,2'-diCl	54	(7)
6	3,3'-diCl	98%, 90°, 1 hr.	4-OH-3,3'-diCl	79	(7)
7	4,4'-diCl	98%, 90°, 1 hr.	2-OH-4,4'-diCl	11	(7)
8	2,2'-diMe	85%, 90°, 30 min.	4-OH-2,2'-diMe	31	(7)
9	3,3'-diMe	85%, 90°, 30 min.	4-OH-3,3'-diMe	52	(7)
10	4,4'-diMe	85%, 90°, 30 min.	2-OH-4,4'-diMe	47	(7)
11	3-Me-3'-NO ₂	98%, 98°, 10 min.	3-Me-3'-NO ₂ -4'-OH	75	(10)
12	3-Cl-3'-Me	98%, 25°, 1 hr.	3-Cl-3'-Me-4'-OH	40	(10)

*: rearrangement induced by diluting a 5 x 10⁻² M solution of the azoxybenzene in aqueous ethanol to five times its volume with 100% H₂SO₄.

Two points concerning these data should be noted: (a) In general, *p*-rearrangement occurs exclusively except with *p,p*-disubstituted azoxybenzenes in which case the *o*-isomer is formed. The anomalous result obtained with 4-methylazoxybenzene could not be satisfactorily explained, especially on an electronic basis, since it is known that the electronic character of the methyl group is intermediate between those of the bromo and methoxy groups. (b) Experiments 1-4 suggest the formation of a symmetrical intermediate since both the α and β isomers yield the same product. On the other hand, experiments 11-12 seem to argue against such an intermediate. This question as to whether the *para*-rearrangement proceeds via a symmetrical or unsymmetrical intermediate was finally resolved by means of experiments with isotopically labelled azoxybenzene.

N^{15} Tracer Studies: In order to determine the direction of hydroxy migration in the absence of substituent effects, Shemyakin and his coworkers (11) studied the rearrangement of azoxybenzene unsymmetrically labelled with N^{15} (X). A synthetic pathway which had previously been developed by Behr (12) was used (Figure 2):

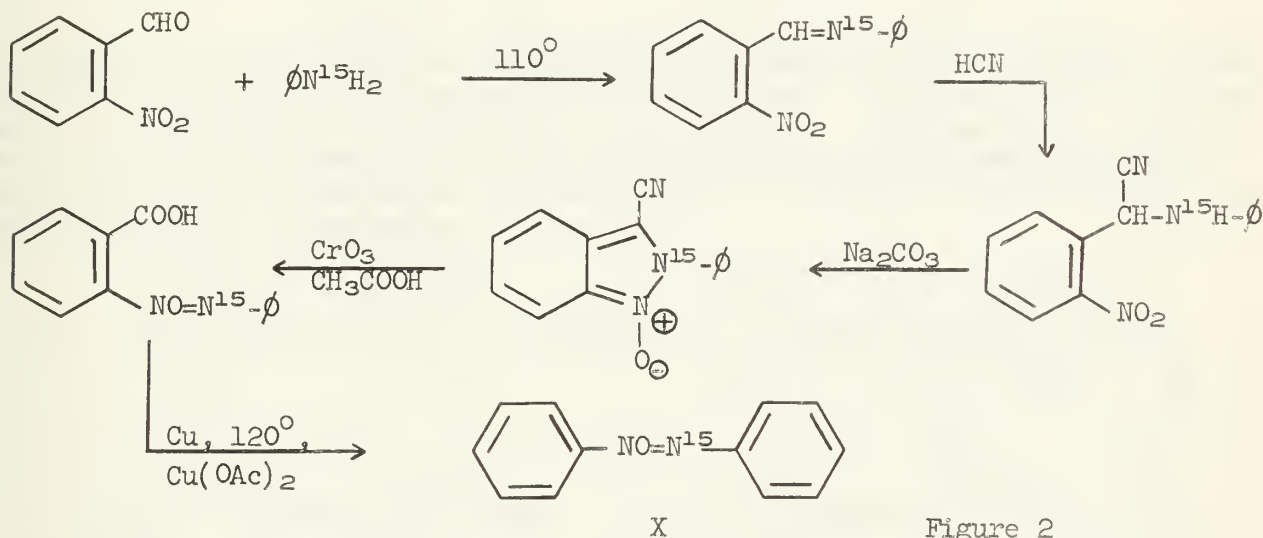


Figure 2

The rearrangements were carried out in chlorosulfonic acid and sulfuric acid under varying conditions. In each case, the distribution of the isotopic label between the two nitrogen atoms in the *p*-hydroxyazobenzene formed as well as in the unreacted azoxybenzene was determined by the degradative procedures outlined in Figure 3:

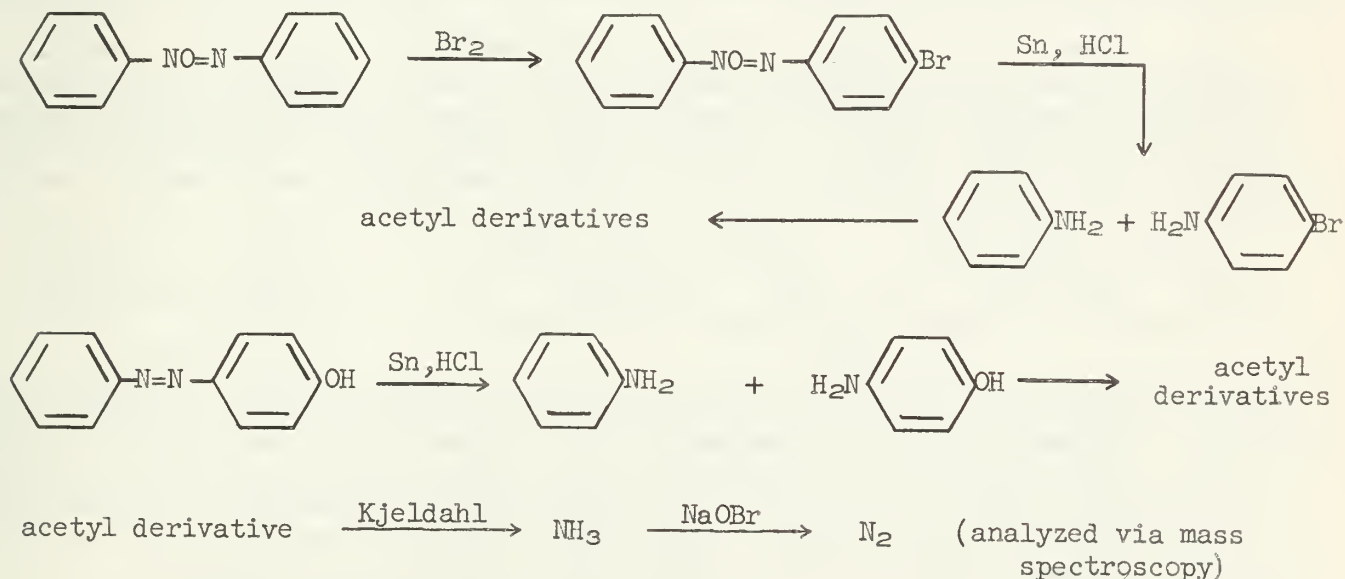


Figure 3

The data obtained in these studies are summarized in Table 2:

TABLE 2: The acid-catalyzed Wallach rearrangement of azoxybenzene- N^{15} (X)

Expt.	Conditions	Excess N^{15} (in atomic %)			
		p-Hydroxyazobenzene		Recovered Azoxybenzene	
		Acetanilide	p-Hydroxy-acetanilide	Acetanilide	p-Bromo-acetanilide
—	—	—	—	0.60	5.06
1	$ClSO_3H$, -8° , 1 hr.	2.75	2.86	—	—
2	$ClSO_3H$, -8° , 1 hr., in the presence of unlabelled azobenzene	2.69	2.75	—	—
3	83% H_2SO_4 , 25° , 8.5 days	2.67	2.88	0.58	5.23
4	83% H_2SO_4 , 90° , 8 min.	2.37	3.08	0.58	5.01
4'	83% H_2SO_4 , 90° , 8 min.	2.83	2.86	0.58	5.01

With the exception of experiment 4, which represents an earlier and apparently erroneous result, it is evident that the rearrangement proceeds with almost complete equalization of the isotopic label between the nitrogen atoms. This indicates the presence of some sort of symmetrical intermediate in the reaction. Azobenzene was ruled out on the basis of the observation that label dilution did not occur to any appreciable extent in experiment 2. Shemyakin thus postulated an N,N -oxide intermediate (XI) and proposed the reaction scheme shown in Figure 4:

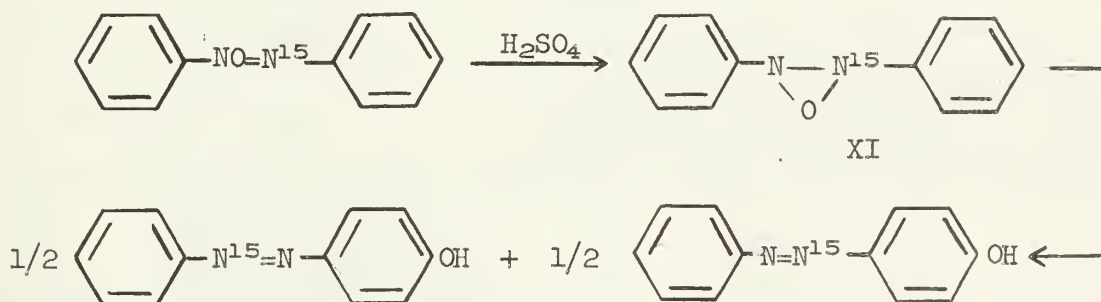
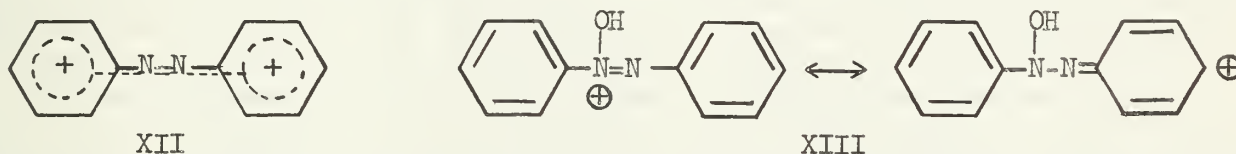


Figure 4

The view that α - β isomerization preceded the rearrangement could be rejected, since the isotopic distribution in the recovered azoxybenzene was shown to be practically unchanged.

In order to account for the small but definite departure from complete label equalization in Shemyakin's data, Gore (13) has suggested that there are actually two mechanisms involved in the para-rearrangement. The major pathway involves a dication intermediate (XII) which, being symmetrical, causes complete equalization of label since it can undergo nucleophilic attack on either ring. An alternative,



less important pathway proceeds by way of a monocation (XIII); nucleophilic attack would be restricted in this case to the ring opposite the N -oxide group. Since it appeared that low-basicity azoxybenzenes should favor the latter pathway, a study was made of the rearrangement (98% sulfuric acid, 23 hours, $20^\circ C$.) of both the α (VI) and β (VII) isomers of p-nitroazoxybenzene to p-nitro-p'-hydroxyazobenzene (VIII). VI rearranged very slowly (4.4% yield of VIII and 95% recovery of VI). VII on the other hand underwent a fast isomerization to VI (53%) and a somewhat slower rearrangement to VIII (46% yield); no unreacted VII was recovered from the reaction

mixture. Shemyakin's mechanism does not account for these findings, but the monocation intermediate suggested by Gore would explain the more facile rearrangement of the β -isomer. Moreover, this study shows that the α - β isomerization can occur under the conditions of the Wallach rearrangement.

In another labelling study (14), azoxybenzene-1- C^{14} in 83% sulfuric acid has been found to rearrange equally to 4- and 4'-hydroxyazobenzene-1- C^{14} , thus further confirming the presence of a symmetrical intermediate in the normal Wallach rearrangement.

O^{18} Tracer Studies: The intermolecular character of the para-rearrangement has recently been demonstrated by Shemyakin and his coworkers through the use of O^{18} tracer methods (15). Rearrangement of $C_6H_5-NO^{18}=N-C_6H_5$ (prepared from azobenzene and $H_2O_2^{18}$) in sulfuric acid and chlorosulfonic acid yielded p-hydroxyazobenzene with essentially no incorporation of O^{18} . Similarly, unlabelled azoxybenzene and several derivatives rearranged in $H_2SO_4^{18}$ to form p-hydroxyazobenzenes which contained a percentage of excess O^{18} very similar to that of the medium. The O^{18} contents of reactants and products were determined as outlined in Figure 5:

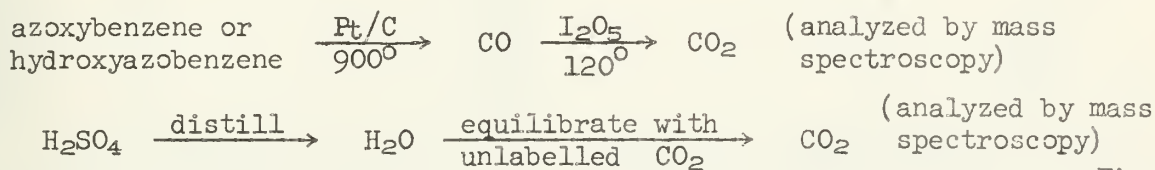


Figure 5

The data obtained from these studies are summarized in Table 3:

TABLE 3: O^{18} studies of the acid-catalyzed Wallach rearrangement

Expt.	Azoxybenzene	Conditions	Excess O^{18} (in atomic %)			
			Initial Azoxybenzene	Medium	Recovered Azoxybenzene	Hydroxy- azobenzene
1	O^{18}	$ClSO_3H, -8^\circ, 1 \text{ hr.}$	1.51	0	—	0.01
2	O^{18}	$83\%H_2SO_4, 23^\circ, 8.5 \text{ days}$	1.51	0	1.49	0
3	O^{18}	$83\%H_2SO_4, 90^\circ, 8 \text{ min.}$	1.51	0	1.54	0.1
4	unlabelled	$83\%H_2SO_4, 23^\circ, 8.5 \text{ days}$	0	0.58	0	0.56
5	unlabelled	$83\%H_2SO_4, 90^\circ, 8 \text{ min.}$	0	0.58	0.01	0.59
6	β - <u>p</u> - NO_2	$98\%H_2SO_4, 23^\circ, 23 \text{ hrs.}$	0	1.02	0*	0.96
7	α - <u>p</u> -Br	$83\%H_2SO_4, 75^\circ, 25 \text{ min.}$	0	1.38	0	1.14
8	<u>m,m'</u> -di NO_2	$93\%H_2SO_4, 140^\circ, 5 \text{ min.}$	0	1.78	0	1.75

*: only α -p-nitroazoxybenzene was recovered

Experiment 6 shows that while the rearrangement itself is apparently intermolecular, the α - β isomerization is intramolecular. This observation was interpreted to be an indication that both isomerization and rearrangement proceed through the previously postulated N,N-oxide intermediate (XI). Shemyakin has maintained that the relative rates of these two reactions depend largely upon the substituent groups present; for azoxybenzene itself, the rate of rearrangement apparently far exceeds the rate of isomerization, whereas for β -p-nitroazoxybenzene the rates are about equal.

Oae and coworkers (16) have also studied the Wallach rearrangement with the aid of O^{18} labelled reagents and have obtained results very similar to those obtained by Shemyakin. An intermolecular mechanism has been proposed by these authors, but unfortunately it involves an unsymmetrical monocation intermediate and thus fails to account for the N^{15} tracer results obtained earlier. The tracer data also indicate that a small but noticeable amount of the oxygen in the hydroxyazobenzene comes from the azoxybenzene used. To explain this, an alternative mechanism involving a bimolecular oxidation was postulated, in which the p-position of one molecule is attacked by the oxygen of a second protonated molecule. Further studies to support this mechanism have not been published.

Kinetics and Miscellaneous Studies: Buncel and Lawton (17) have recently pre-

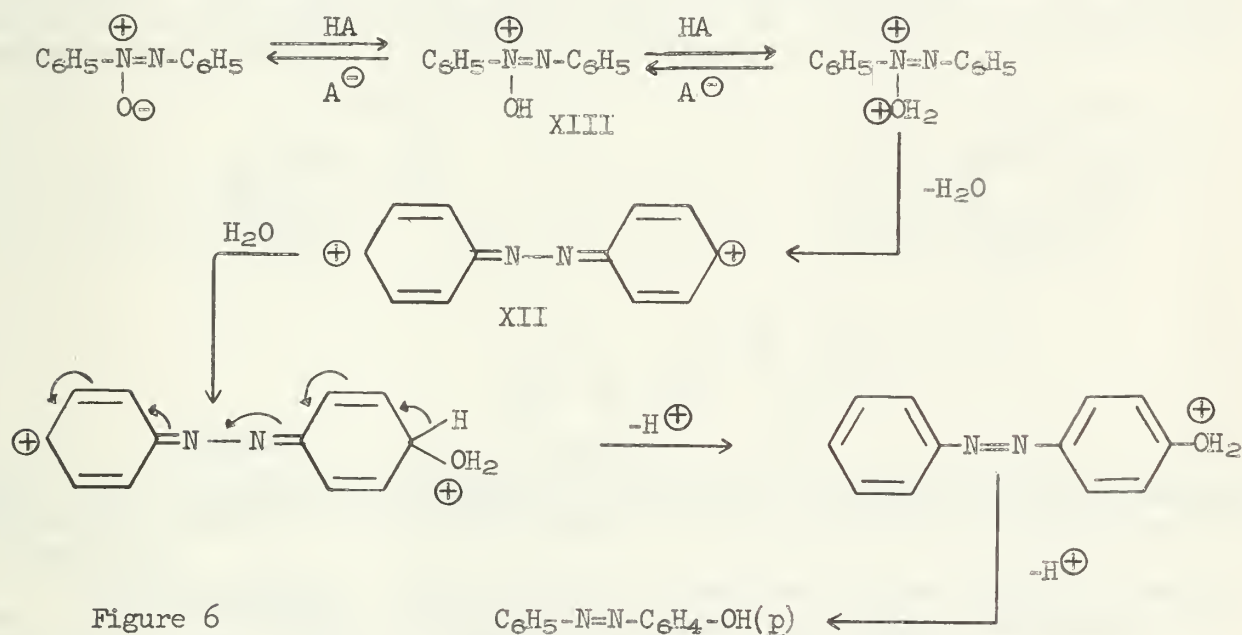
sented kinetic evidence in support of Gore's postulated dication intermediate (XII). The rearrangement of azoxybenzene in varying concentrations of sulfuric acid at 25°C. was followed spectrophotometrically and found to be first-order in azoxybenzene; the data obtained are summarized in Table 4:

TABLE 4: Kinetics of the Wallach rearrangement of azoxybenzene at 25°C.

% H ₂ SO ₄	$\frac{[\text{Azoxybenzene H}^{\oplus}]}{[\text{Azoxybenzene}] + [\text{Azoxybenzene H}^{\oplus}]}$	* 10 ⁵ x k (sec ⁻¹ at 25 ^o)
75.30	0.946	0.016
77.45	0.972	0.048
80.15	0.986	0.208
82.87	0.994	0.778
85.61	0.997	2.17
87.57	0.999	3.68
90.37	1.000	7.23
92.80	1.000	11.6
95.19	1.000	20.9
96.40	1.000	26.1

*: calculated from $pK_a = H_0 + \log [Azoxybenzene H^+]/[Azoxybenzene]$

The azoxybenzene is seen to be almost completely monoprotated even at the lowest concentration of hydrogen ion. The fact that the rate varies greatly with the acid concentration while the extent of monoprotation remains fairly constant suggests that a second proton transfer is involved in the rate determining step. On this basis the authors proposed the following mechanism (Figure 6):



A plot of log k vs. -H₀ gave two straight lines, the first with slope 1.7, the second with slope 0.8; the break in the curve occurred at a -H₀ value corresponding to sulfuric acid monohydrate. The authors were unable to explain satisfactorily this deviation from the expected linear plot. However, it has been reported (18) that the rate of the acid-catalyzed hydrolysis of amides decreases at very high concentrations of acid due to the decreased concentration of water. For the Wallach rearrangement, it is thus conceivable that above a certain acid concentration the deficiency of water becomes an important secondary factor and affects the normal increase in rate with -H₀ in a negative manner.

Duffey (14) has investigated the kinetics of the para-rearrangements of several

substituted azoxybenzenes and found that electron-withdrawing substituents decrease the rate of rearrangement. Although more data are needed for a meaningful Hammett plot, it is evident that the reaction has a negative ρ -value.

Cryoscopic studies (14) indicate that in 100% sulfuric acid azoxybenzene yields about four particles per molecule while in 85% sulfuric acid only two particles are formed. This observation would support the theory of the dication intermediate except for the fact that studies of ultraviolet spectra suggest that in 100% sulfuric acid the conjugate acid of *p*-hydroxyazobenzene is formed "immediately" from azoxybenzene. An attempt to resolve this conflict of observations by means of conductivity studies is now in progress.

The Ortho-Rearrangement:

Early Work: In 1903, Knipscheer (19) found that under certain conditions azoxybenzene could be made to rearrange predominantly to *o*-hydroxyazobenzene. For example, azoxybenzene (in the solid state or in benzene solution) exposed to sunlight for six weeks rearranged to *o*-hydroxyazobenzene in 10% yield with no detectable traces of the *p*-isomer. Similar results were observed upon heating azoxybenzene in an atmosphere of carbon dioxide or with acetic anhydride.

Azoxynaphthalenes have been found to undergo photochemical rearrangement to azonaphthols (20). By comparison with authentic samples, it was shown that in the case of α,α' -azoxynaphthalene the hydroxy group migrates to the β -position of the naphthalene ring; similarly, migration to the α -position is observed during the rearrangement of β,β' -azoxynaphthalene. In fact, studies of the light-catalyzed Wallach rearrangements of various substituted azoxybenzenes (21) indicate that this migration to the *o*-position is a general phenomenon. Higher temperatures improve the yield only slightly. The nature of the solvent, on the other hand, plays a more important role, higher yields being obtained in more polar solvents.

Badger and Buttery (22) investigated the ortho-rearrangement of unsymmetrically substituted azoxybenzenes (ultraviolet light, one month, in benzene) and found that in all the cases studied the oxygen migrated to the far ring. An intramolecular mechanism was proposed to account for this (Figure 7):

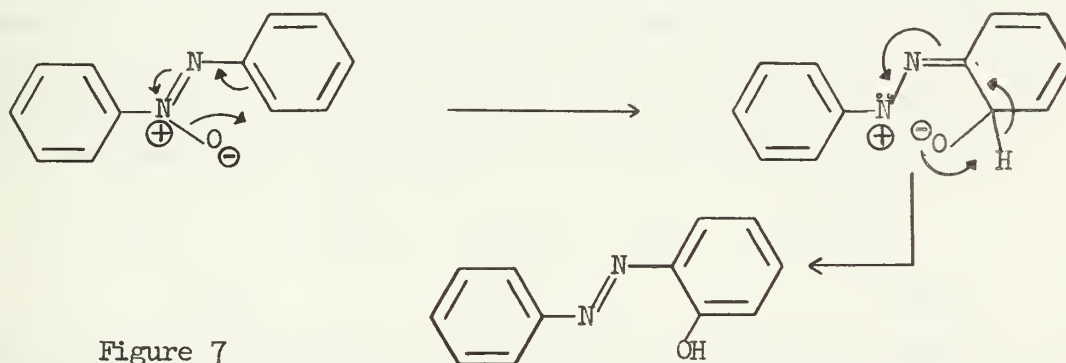


Figure 7

This ionic mechanism was postulated in preference to a similar radical mechanism presumably because of the large dependence of the rate of the reaction upon the solvent used.

N¹⁵ Tracer Studies: Using the same techniques outlined earlier, Shemyakin (11) has studied the direction of hydroxy migration in the ortho-rearrangement of $\text{C}_6\text{H}_5\text{-NO=N}^{15}\text{-C}_6\text{H}_5$. The data obtained are summarized in Table 5:

TABLE 5: The ortho Wallach rearrangement of azoxybenzene- N^{15} (X)

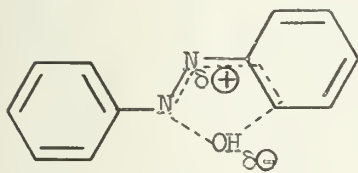
Expt.	Conditions	Excess N^{15} (in atomic %)			
		<i>o</i> -Hydroxyazobenzene		Recovered Azoxybenzene	
		Acetanilide	<i>o</i> -Hydroxy-acetanilide	Acetanilide	<i>p</i> -Bromo-acetanilide
1	UV, 85% EtOH, 65 hrs., 30-45°	0.6	4.93	0.60	5.06
2	UV, 85% EtOH, 65 hrs., 30-45°	0.6	4.93	0.99	4.75
3	UV, 85% EtOH, 65 hrs., 30-45°	0.6	4.93	0.70	5.08
3	$\text{CH}_3\text{COOCOCH}_3$, 4 hrs., 230-240°	0.75	4.88	0.63	5.11

It is evident that in contrast to the para-rearrangement, there is little equalization of isotopic label in the ortho-rearrangement. Although these data in general support the Badger-Buttery mechanism, the small but definite amount of label equalization in all the experiments suggests that a secondary process is also occurring. Shemyakin proposed a reversible light-catalyzed isomerization proceeding through an N,N-oxide intermediate to account for this minor equalization.

O¹⁸ Tracer Studies: Shemyakin (15a) also showed that the ortho-rearrangement is intramolecular in character through the use of O¹⁸ labelled reagents. The experimental methods involved have been outlined earlier; the results of this study are shown in Table 6:

TABLE 6: O¹⁸ studies of the ortho Wallach rearrangement

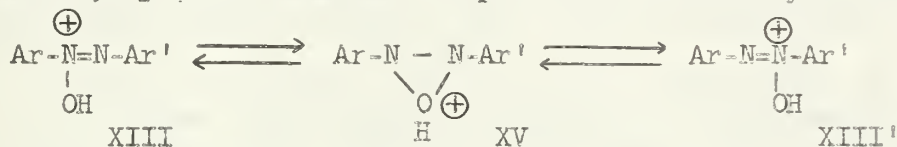
Expt.	Azoxybenzene	Conditions	Excess O ¹⁸ (in atomic %)			
			Initial Azoxybenzene	Medium	Recovered Azoxybenzene	Hydroxyazobenzene
1	O ¹⁸	UV, 85% EtOH, 65 hrs., 30-45°	1.51	0	1.51	1.53
2	unlabelled	O ¹⁸ -labelled Ac ₂ O, 4 hrs., 230-240°	0	0.51	0	0



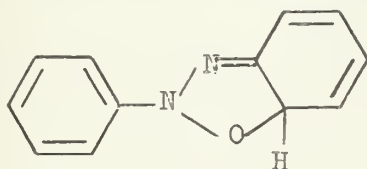
XIV

Oae and his coworkers (16) have recently performed similar O¹⁸ tracer experiments and obtained results which confirm Shemyakin's findings. These authors, however, prefer to regard the photochemical mechanism as involving an intramolecular oxygen radical shift from the N-oxide group. Moreover, for the non-photochemical ortho-rearrangement they postulate an intimate ion-pair intermediate (XIV).

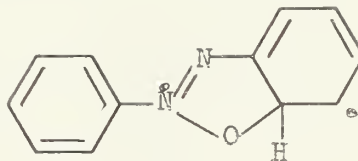
Conclusions: In spite of the considerable amount of data that has been accumulated on the Wallach rearrangement, it cannot be said that the mechanism of this reaction has been established with certainty. With regard to the para-rearrangement, it seems that the scheme proposed by Buncl and Lawton (Figure 6) fits the data best. To account for the observed intramolecular isomerization of some azoxybenzenes, an additional step might be proposed, namely the equilibration of the two isomeric forms of monocation XIII by way of a protonated cyclic intermediate (XV). Then, as Shemyakin has proposed, the relative rates of rearrangement and isomerization would depend in some way upon the substituents present on the azoxybenzene.



For the ortho-rearrangement, the mechanism postulated by Badger and Buttery (Figure 7) seems reasonable, but the question of whether the mechanism is actually ionic or radical has yet to be answered. The possibility of cyclic intermediates such as XVI and XVII should not be discounted either. To complicate matters further,



XVI



XVII

Jaffe (23) has recently found that the photochemical rearrangement does not occur readily, especially when the azoxybenzene used is very pure, and that cis-trans isomerization and other photochemical transformations occur in preference to the Wallach rearrangement. Thus it is evident that there are still many questions to be answered with regard to this reaction.

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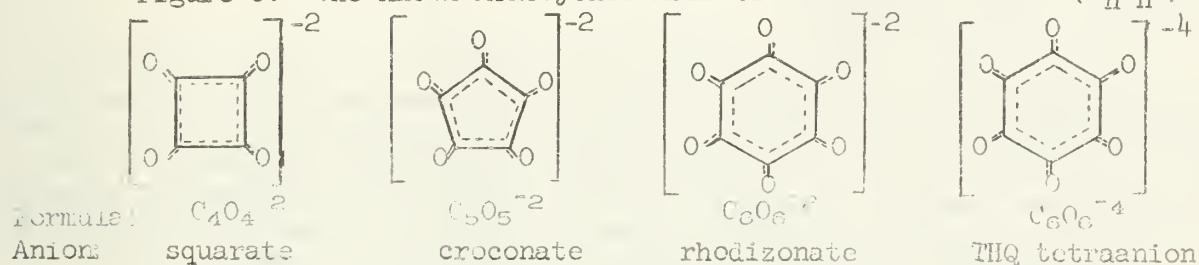
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MONOCYCLIC AROMATIC OXOCARBON ANIONS ($C_nO_n^{m-}$)

Reported by Thomas P. Doherty

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Introduction.--An aromatic compound, for the purposes of this discussion, is defined theoretically as being any cyclic species possessing additional bonding energy resulting from a delocalization of electrons around the entire ring; thus forming a cyclically conjugated system from electrons which were originally constrained to isolated double bonds in a hypothetical molecule. Unfortunately, the very possession of this "delocalization energy" is very difficult to measure experimentally; consequently, it is sometimes difficult to make a sharp distinction between the aromatic and alicyclic series of organic compounds. This distinction has become of major importance with the recent recognition of non-benzenoid, cyclically-conjugated systems (1) which possess benzenoid properties. One of these newly recognized systems is that of the monocyclic aromatic oxocarbon anions ($C_nO_n^{m-}$). Oxocarbons are "organic molecules or ions in which all, or nearly all, of the carbon atoms bear ketonic oxygen functions or their equivalents" (2). They are analogous to hydrocarbons, fluorocarbons, and cyanocarbons. At this time, only four compounds in the $C_nO_n^{m-}$ series are known (Figure 1)--the squarate, croconate, and rhodizionate dianions and the tetraanion from tetrahydroxyquinone (THQ) (2). This abstract in-

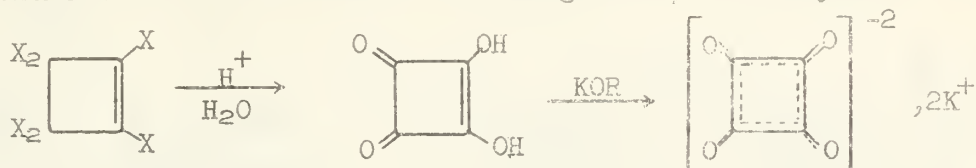
Figure 1: The Known Monocyclic Aromatic Oxocarbon Anions ($C_nO_n^{m-}$)

cludes a discussion of organic and inorganic syntheses, X-ray crystal structure proofs, group theoretical predictions of infrared and Raman spectral bands, and the results from LCAO-MO calculations of delocalization energies, bond orders, and charge densities of the monocyclic aromatic oxocarbon anions ($C_nO_n^{m-}$). A discussion of some of the chemical reactions and of the varied analytical and biochemical applications of these species is also included.

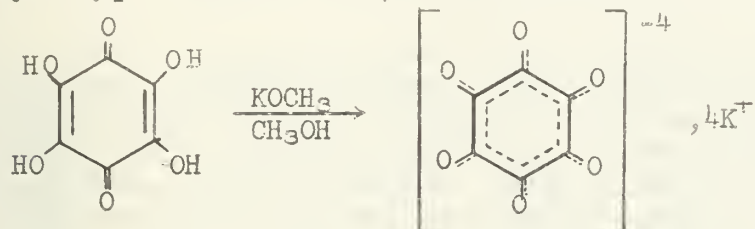
Syntheses.--Although the monocyclic oxocarbon anions of the $C_nO_n^{m-}$ series have just recently been recognized as "a new class of aromatic substances" (3), the croconate anion and the rhodizionate anion were discovered more than 140 years ago. During the summer of 1823, Berzelius, Wöhler, and Kindt noticed that a black powdery residue was formed during the preparation of potassium (4) by the reduction of potassium hydroxide with carbon (5). From this black powdery residue, Gmelin (4) and Liebig (6) isolated the croconate anion, and Heller (7) isolated the rhodizionate anion. Both anions were isolated in the form of their potassium salts. The croconate and rhodizionate anions were then obtained in higher yields by passing dry carbon monoxide over heated potassium, producing a compound of the formula $K_6C_6O_6$ which was oxidized to both the rhodizionate and croconate anions upon exposure to moist air (6,7). Since it is now known that croconic acid may be produced from rhodizonic acid by air oxidation (8), the rhodizionate anion may be an intermediate in the conversions of $K_6C_6O_6$ to potassium croconate; surprisingly, this situation was proposed by Heller (7) as early as 1837. Another interesting aspect of the early work might now be mentioned. Since croconic acid is thought to be one of the products obtained from the action of the *P. beijerinckii* bacterium on hexahydroxycyclohexane (meso-inositol) (8,9), a substance commonly found in plants and animals, Gmelin's preparation (4) of croconic acid in 1825 may well have been the first (although unrecognized as such) preparation of an organic compound from purely inorganic starting materials. Wöhler's classical synthesis of urea (10) was not published until 1828, three years later.

Modification of these initial syntheses are still used for the preparation of the croconate and rhodizionate anions (8). Croconic acid can be prepared by the oxidation of a variety of polyhydroxybenzene derivatives. An example of this type of synthesis is the oxidation of tetrahydroxyquinone or rhodizonic acid with manganese dioxide (8). Rhodizonic acid is usually obtained from the self-condensation of aqueous glyoxal in the presence of oxygen (8).

In 1959, Park, Cohen, and Lacher (11) prepared potassium squarate in nearly quantitative yield by the hydrolysis in 50% aqueous sulfuric acid of 1,2-diethoxy-3,3,4,4-tetrafluorocyclobutene, followed by treatment with potassium hydroxide or alkoxide. The general scheme is shown below where X = halogen and/or alkoxyl:



The anion $C_6O_6^{4-}$ was obtained by West and Niu (12) directly from the known tetrahydroxyquinone (THQ) (12,13) by treatment with potassium methoxide in methanol:



West and coworkers appeared to assume (2,12) that they were the first to prepare the $C_6O_6^{4-}$ anion. However, it is very likely that the anion was actually first prepared by Lerch (13) over one hundred years earlier, and later described by Nietzku and Benckiser (14).

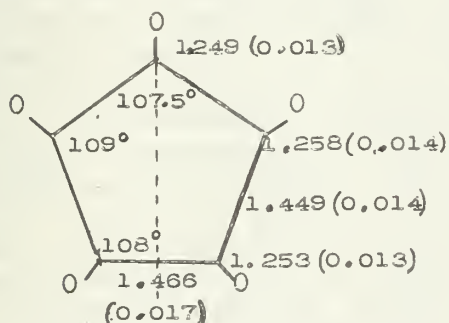
The $K_6C_6O_6$ species, which was named hexapotassium hexahydroxybenzene by Lerch (16) in 1834, may be another member of this series—the $C_6O_6^{6-}$ anion. Evidence also exists (12) for the radical trianion, $C_6O_6^{3-}$. Partial oxidation of $K_4C_6O_6$ in ether produces a green, strongly paramagnetic solid with an ESR peak near $g = 2.003$. Further oxidation of this green solid produces potassium rhodizonate ($K_2C_6O_6$). To date, the $C_3O_3^{2-}$ anion has not been prepared; however, it would be interesting to investigate the reaction product from the acid hydrolysis of tetrachlorocyclopropene (15) for this species.

Although only the potassium salts of the oxocarbon anions have thus far been discussed in this abstract, several divalent and some trivalent metal complexes contain these anions as ligands. These complexes are conveniently prepared by adding a metal salt (e.g. the Cl^- , SO_4^{2-} , or NO_3^-) to an aqueous solution of the potassium oxocarbon anion. Most of these metal complexes appear to be polymeric in nature (16,17). The structure proof of the geometry and bonding of these aromatic oxocarbon anions lies mainly in the X-ray crystal structure and the vibrational spectral studies. (*vide infra*)

Crystal Structures.—Although mainly polymeric squarate and croconate complexes have been studied by X-ray crystallographic methods, three monomeric species have also been studied.

Monomeric diammonium croconate was found (18) to possess a nearly planar croconate anion (Figure 2), with the largest deviation of any atom from the plane being 0.024 Å.

Figure 2: The X-ray Structure of the Croconate Anion in Diammonium Croconate (18)^a

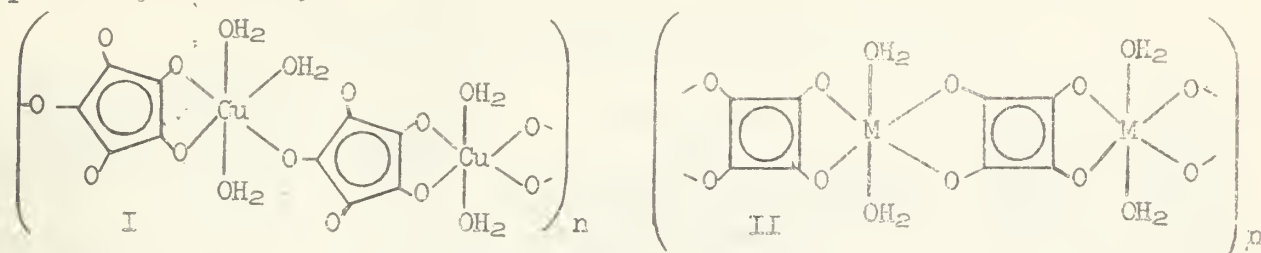


a. The dotted line indicates a mirror plane; and the standard deviations of the bond orders appear in the parentheses.

The crystal structures of ammonium hydrogen croconate ($NH_4HC_5O_5$) (18) and rubidium hydrogen croconate ($RbHC_5O_5$) (19) also possess nearly planar croconate anions, the largest deviation from the plane being 0.12 Å (18). In these latter two cases, the croconate anions appear to be connected by strong intermolecular H-bonds (18).

Complete three-dimensional X-ray diffraction studies on polymeric copper croconate trihydrate ($CuC_5O_5 \cdot 3H_2O$)_n have shown (20,21) that the copper cations are surrounded by six oxygen atoms at the corners of a distorted octahedron (I). The similarities of the X-ray powder patterns of the croconates of divalent Fe, Zn, Ni, Mn, and Co with that of copper croconate suggests (16) that the entirety form an isostructural series. The X-ray powder pattern of calcium croconate differs from that of the others, thus implying different crystal structures. The polymeric croconates of trivalent Al, Fe, and Cr show nearly identical X-ray powder patterns, thus suggesting another

isostructural series. A preliminary X-ray crystal study of the chromium (III) complex (21) shows evidence for the empirical formula $\text{Cr}_2(\text{C}_5\text{O}_5)_4(\text{OH})_7(\text{H}_2\text{O})_{16}$. It is obvious that any conclusion as to the structure of the trivalent croconates must await a complete crystal study.



The X-ray powder patterns of the polymeric divalent Mn, Fe, Co, Ni, Mg, and Zn squarates, having the general formula $[\text{MC}_4\text{O}_4 \cdot 2\text{H}_2\text{O}]_n$, are identical except for slight differences in lattice spacing with a change in the metal radius (12). These results suggest that the crystal packings of these divalent squarates are isomorphous and imply that these divalent squarates "form an extensive isostructural series" (17). An absolute conclusion, however, must await a complete three-dimensional X-ray diffraction study. The IR spectra of these divalent squarates indicate symmetries not appreciably different than D_{4h} . An octahedrally coordinated geometry (II) is consistent with these data. The squarate dihydrates of divalent Ca and Cu show different powder patterns and additional IR bands, a situation which would seem to indicate a less symmetrical structure for these compounds than for those of the other metals mentioned. Polymeric squarate complexes of trivalent Al, Fe, and Cr, having the general formula $[\text{MC}_4\text{O}_4(\text{OH}) \cdot 3\text{H}_2\text{O}]_n$, show nearly identical X-ray powder patterns, a situation which implies that these trivalent squarates also form an isostructural series.

In general, the apparent high symmetry of the oxocarbon anions, indicated by the X-ray work, suggests that these anions contain delocalized electrons which make the carbons, and similarly the oxygens, equivalent to each other, a situation which gives aromatic character to the molecules.

Vibrational Spectroscopy.—Several studies of the infrared spectra of the known oxocarbon anions have appeared in the literature (3,11,12,22,23); however, only the spectra of the squarate and the croconate anions have been studied extensively (23). Vibrational assignments of the IR and Raman spectral frequencies for the squarate and croconate anions were proposed on the bases of the planar symmetrical structures— D_{4h} and D_{5h} respectively—and on the basis of a normal coordinate treatment using a Urey-Bradley force field (24). A comparison of the theoretically computed results with the experimentally observed frequencies for the squarate anion appears in Table I, while that for the croconate anion appears in Table II. The average deviation of the calculated frequencies from those observed is approximately 1.5% for the squarate anion and 1.6% for the croconate anion. It is to be noted that seven Raman active fundamentals (two of which are polarized), four infrared active fundamentals, and no coincidences of Raman and infrared fundamentals are predicted in both cases (see "Selection Rule" column in Tables I and II). In fact, any anion of the $\text{C}_n\text{O}_n^{\text{--m}}$ series is predicted to have the same number of spectral bands if a symmetrically planar structure is assumed (23). The combination or overtone frequencies, which are listed below the normal vibrational frequencies in Tables I and II, might instead be frequencies due to slight deviations from planarity. This view is supported by the observation that more "extra" bands occur in the spectrum of the croconate anion which probably has the more flexible ring. Further support is provided from the facts that two of the Raman active depolarized fundamentals were not observed for croconate and also that all these "extra" bands are IR active. However, if models less symmetrical than D_{4h} and D_{5h} are chosen (such as C_{2h} and D_{2d}), many more frequencies are predicted. Thus it is concluded that the chosen symmetries are nearly correct (23), a conclusion which has already been reached by earlier workers (11,22). Even though this result is based on several assumptions and negative evidence, it appears to be reliable.

Less thorough studies have been made on the hexacarbon anions, partly because their highly colored solutions make it difficult to determine their Raman spectra. However, the results seem to indicate that the rhodizonate anion ($\text{C}_6\text{O}_6^{2-}$) has a nearly

symmetrical planar geometry (D_{6h}) (3), and that the THQ tetraanion ($C_6O_6^{4-}$) exists in a slightly puckered chair form of D_{3d} symmetry (12).

Table I: Comparison of the Theoretical and Experimental Results for the Squarate ($C_4O_4^{2-}$) Anion (23).

Number of Normal Vibration	Symmetry Species (D_{4h})	Selection Rule ^a	Vibrational Mode	$\nu_{obsd.}^a$ (cm^{-1})	ν_{calc} (cm^{-1})	Deviation (%)
ν_1	A_{1g}	R (p)	Symmetrical CO stretching	1794 w,p	1778	-0.9
ν_2			Ring breathing	723 s,p	730	+1.0
ν_3	A_{2g}	Inactive	In-plane CO bending	---	--	--
ν_4	A_{2u}	IR	Out-of-plane CO bending	259 s	--	--
ν_5	B_{1g}	R (dp)	CC stretching	1123 vs,dp	1128	+0.5
ν_6			In-plane CO bending	294 w,dp	299	+1.7
ν_7	B_{1u}	Inactive	Out-of-plane CO bending	---	--	--
ν_8			Ring twisting	---	--	--
ν_9	B_{2g}	R (dp)	CO stretching	1593 s,dp	1633	+2.5
ν_{10}			Ring bending	647 s,dp	635	-1.9
ν_{11}	E_g	R (dp)	Out-of-plane CO bending	(662) vw	--	--
ν_{12}	E_u	IR	CO stretching	1530 vs,vb	1544	+1.0
ν_{13}			CC stretching	1090 s	1070	-1.8
ν_{14}			In-plane CO bending	350 m	354	+1.1
$\nu_2+\nu_{11}$		R		1329 vw	--	--
		IR		1700 vw	--	--
$\nu_5+\nu_{13}$		IR		2200 w	--	--

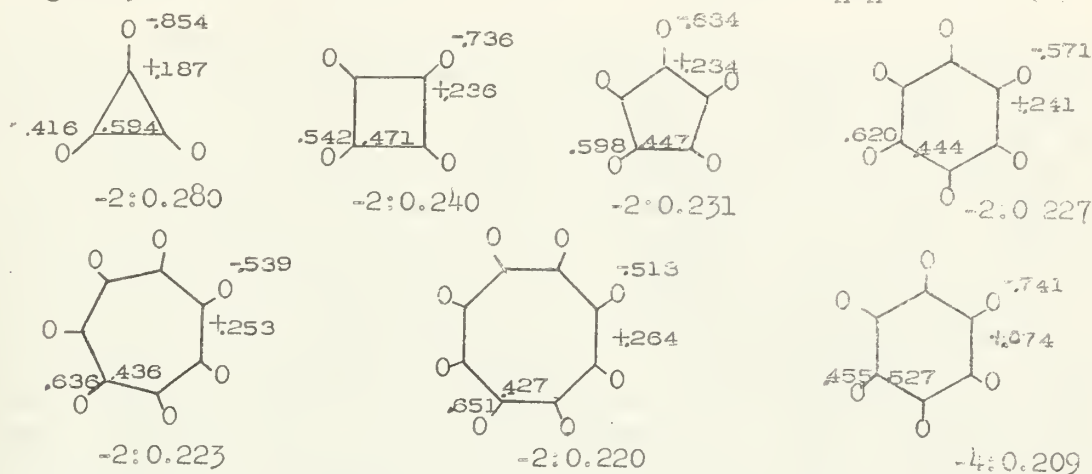
Table II: Comparison of the Theoretical and Experimental Results for the Croconate ($C_5O_5^{2-}$) Anion (23).

Number of Normal Vibration	Symmetry Species (D_{5h})	Selection Rule ^a	Vibrational Mode	$\nu_{obsd.}^a$ (cm^{-1})	$\nu_{calc.}$ (cm^{-1})	Deviation (%)
ν_1	A_1'	R (p)	Symmetrical CO stretching	1718 w,p	1652	-3.8
ν_2			Ring breathing	637 m,p	655	+2.8
ν_3	A_2''	Inactive	In-plane CO bending	---	--	--
ν_4	A_2''	IR	Out-of-plane CO bending	248 s	--	--
ν_5	E_1'	IR	CO stretching	1570 vs,vb	1605	+2.2
ν_6			CC stretching	1100 w	1087	-1.2
ν_7			In-plane CO bending	374 m	372	-0.5
ν_8	E_1''	R (dp)	Out-of-plane CO bending	---	--	--
ν_9	E_2'	R (dp)	CO stretching	1591 s,dp	1584	-0.4
ν_{10}			CC stretching	1243 m,dp	1223	-1.6
ν_{11}			Ring bending	555 s,dp	558	+0.5
ν_{12}			In-plane CO bending	---	357	--
ν_{13}	E_2''	Inactive	Ring twisting	---	--	--
ν_{14}			Out-of-plane CO bending	---	--	--
		IR		350 vw		
$\nu_4+\nu_{11}$		IR		795 w		
		IR		1325 w		
$\nu_{11}+\nu_6$		IR		1660 w		
$\nu_2+\nu_6$		IR		1740 w		
$\nu_5+\nu_{11}$		IR		2120 vw		
$\nu_5+\nu_9$ or $2 \times \nu_5$		IR		3150 vw		

^a Abbreviations: b=broad, dp=depolarized, IR=infrared, m=medium, p=polarized, R=Raman, s=strong, v=very, w=weak

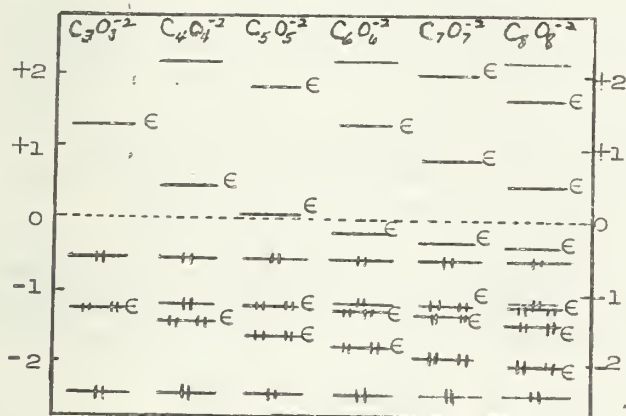
LCAO-MO Calculations.--West and Powell (2) have calculated delocalization energies, bond orders, and charge densities by the Hückel LCAO-MO method (1) for the anions of the $C_nO_n^{m-}$ series where $m=2$ for $n=3$ to 8 and $m=4$ for $n=6$ (Figure 3). Below each diagram, the charge on each anion and the delocalization energy per π -electron (DE/π) in units of β are indicated. Numbers with positive or negative signs within the diagrams design-

Figure 3: Results of LCAO-MO Calculations on the $C_nO_n^{m-}$ Series (2)



ate net charges on atoms, and those with no signs denote π -bond orders. Energy levels for the $C_nO_n^{2-}$ series where $n=3$ to 8 were also calculated (Figure 4).

Figure 4: π -Electron Energy Levels for the $C_nO_n^{m-}$ Series (2)^a



^a ϵ indicates a doubly degenerate energy level.

For these calculations, a few refinements (2) were incorporated into the simple Hückel LCAO-MO method (1). The hypothetical reference structures chosen for the calculations were those with their negative charges localized on the oxygen atoms. (e. g. $O = \triangle O^-$ was chosen as the reference

structure for $C_3O_3^{2-}$.) The parameters for the coulomb and resonance integrals were chosen as $k_{CC}=1$, $l_{CO}=0.8$, $h_O=1$. The use of different "widely spaced parameters" (2) did not result in significantly different delocalization energies. Moreover, calculations using the ω -method and the SCF-MO methods "gave poorer agreement with experimental data" (2). Before discussing the results of these calculations, it is beneficial to consider a quote from Streit-

wieser's book (1): "Actually, the inherent assumptions of the [Hückel MO] method are so unrealistic we marvel that the theory finds any use at all!" Furthermore, in the case of the oxocarbons, it appears that, in large, the approximations chosen were those which more nearly agreed with the experimental data.

A comparison of the results from Figures 3 and 4 allows several qualitative relationships to be stated. As the ring size increases, carbon-oxygen bond orders are predicted to increase while carbon-carbon bond orders and delocalization energies per π -electron are predicted to decrease. These predictions suggest a large stability for the yet unknown anion $C_3O_3^{2-}$ and the $C_4O_4^{2-}$ anion. A qualitative comparison of these predicted thermodynamic stabilities with some experimental data has been made by West and coworkers (2,3), who used the acid dissociation constants of the enediols (Table III). Since a lower pK_a suggests a stronger acid (hence a more stable anion), the results in Table III would suggest (3) a slight decrease in stability of the anion as the ring size increases. However, there appears to be some disagreement in the literature over the pK 's for croconic acid. Yamada, Mizuno, and Hirata (22) using ultraviolet spectral methods showed that the pK_1 and pK_2 for croconic acid are > 1 and

Table III: Acid Dissociation Constants of the Known Enediols ($H_2C_nO_n$) in Water (3)

	pK_1	pK_2	Method of Measurement	Reference
$H_2C_4O_4$	1	2.2-3.0	----	11
$H_2C_5O_5$	2.17(?)	4.0(?)	potentiometric	25
$H_2C_6O_6$	3.15	4.9	potentiometric, UV	26

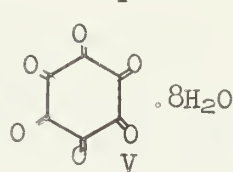
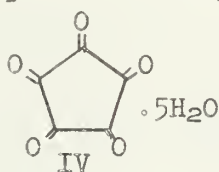
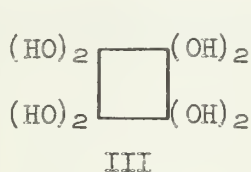
1-2 respectively. These data have been supported by Carlqvist and Dyrssen (27) who, using both ultraviolet and potentiometric methods, have shown that the pK_1 and pK_2 for croconic acid are 0.2-0.3 and 1.3-1.5 respectively. It appears that Carpeni's figures (25) are in error. Upon insertion of the newer pK values into Table III, the croconate ion would be predicted to be the most stable of the three anions. However, the LCAO-MO theory predicts the squarate ion to be the most stable of the three. This disagreement forces the conclusion that no correlation of thermodynamic stabilities with acid dissociation constants is possible at this time. However, the fact that the enediols are very acidic suggests that the respective anions possess aromatic character.

In Figure 4, it can be seen that while the lowest unfilled orbital is antibonding for $n \leq 5$, its energy is predicted to decrease with increasing ring size so that the orbital becomes bonding for $n \geq 6$. This observation leads to the prediction that polyanions of the series $C_nO_n^{m-}$ where $m = 3$ to 6 can be prepared as stable entities if $n \geq 6$.

Although the authors (2) admit that calculations of this sort are highly approximate, the qualitative relationships that are obtained from such calculations have long given impetus to the preparation of non-benzenoid aromatic compounds. Such has been the case in the field of aromatic oxocarbons. Although the calculations were made after the syntheses of the squarate, croconate, and rhodizonate anions, they led directly to the successful synthesis of the tetrapotassium salt from tetrahydroxyquinone ($K_4C_6O_6$) (2). It is interesting that the latter is diamagnetic, in direct contrast to the prediction of Hund's rule (1), which predicts a degenerate, paramagnetic triplet state (see Figure 4). However, the presence of electron correlation effects, neglected (2) in the LCAO-MO calculations, might operate to remove this degeneracy.

Some Chemical Reactions.---The aromatic oxocarbons undergo several chemical reactions, the most interesting of which will be mentioned below.

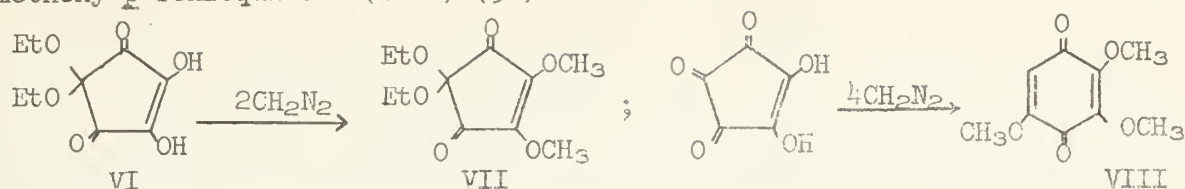
A comparison of the products from the nitric acid oxidations of the enediols proves to be interesting. Upon treatment with dilute nitric acid, squaric acid, croconic acid, and rhodizonic acid yield octahydroxycyclobutane (III) (28), leuconic acid pentahydrate (IV) (29), and triquinoyl octahydrate (V) (13), respectively (8). The infrared spectrum of III shows no peaks above 1300 cm^{-1} except the OH stretching mode



(3250 cm^{-1}). Together, the infrared and Raman suggest that III possesses D_{4h} symmetry (28). Similar spectra are obtained for IV and V (8), except that leuconic acid pentahydrate (IV) gives a weak intensity peak at 1625 cm^{-1} , and triquinoyl octahydrate (V) gives a medium intensity peak at 1650 cm^{-1} (28). These results might indicate that the keto forms are in equilibrium with their respective perhydroxy forms $[C_n(OH)_{2n}]$: $C_nO_n + nH_2O \rightleftharpoons C_n(OH)_{2n}$. As the ring size becomes smaller than six, the equilibrium might shift in favor of the perhydroxy form since ring strain would inhibit the smaller rings from "bearing the burden" of the keto groups. However, the "carbonyl" bands might simply be due to a normal vibrational frequency from a symmetry lower than D_{5h} or D_{6h} , or to an overtone or combination band. Regardless, it appears that the perhydroxy forms are favored; consequently, the structures originally proposed for IV and V appear to be in error.

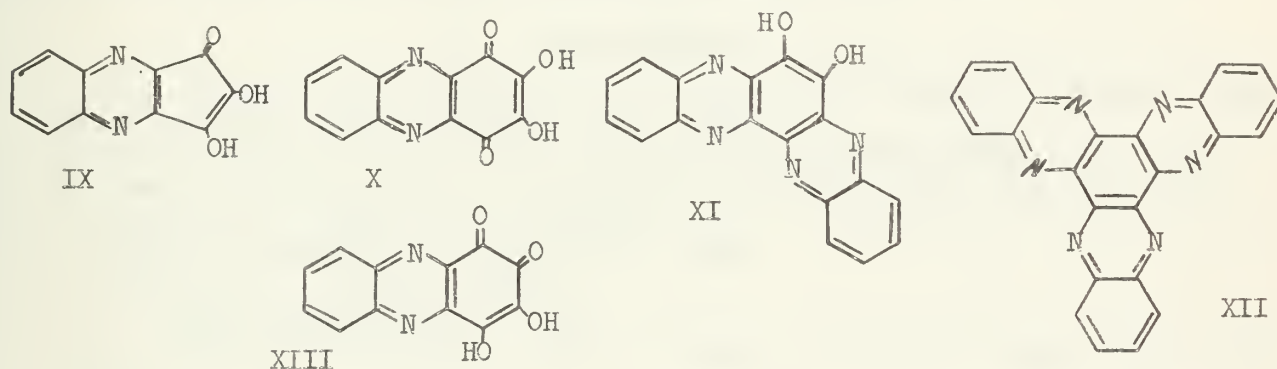
An interesting anomaly arises from the reaction of diazomethane with the diethyl acetal of croconic acid (VI) and with croconic acid. Under this treatment, VI is simply converted into its dimethyl ether (VII) (30); whereas croconic acid consumes four moles of diazomethane and is converted into the ring enlargement product, tri-

methoxy-p-benzoquinone (VIII) (31):



The structure of VIII was proven by comparison with an authentic sample which was synthesized from pyrogallol. VII was also independently synthesized by treating the silver salt of VI with methyl iodide in absolute ether (30). Under the same treatment, silver croconate was converted into its dimethyl ether, a compound which was significantly different from VIII. These results can be rationalized with the consideration that croconic acid appears to possess more ring strain than its diethyl acetal; consequently, croconic acid benefits more from ring enlargement.

Sodium rhodizonate has been found to form addition compounds with benzidine, hexamminecobalt, and hexamminechromium (32). The latter two probably have structures similar to the aquo complexes with ammonia molecules in place of the water molecules. Moreover, *o*-phenylenediamine gives a 1:1 addition compound (IX) with croconic acid and 1:1 (X), 2:1 (XI), and 3:1 (XII) addition compounds with rhodizonic acid (33). All these products were identified on the basis of their elemental analyses, infrared spectra, and chemical reactions as well as by the fact that XII is a known compound. Nonetheless, there appears to be no evidence that would rule out structure XIII for the 1:1 addition compound with rhodizonic acid.



Analytical Applications.--Because of their striking colors, the derivatives of croconic acid, and especially those of rhodizonic acid, have been used as analytical indicators for several years. In fact, the word "rhodizonic" was taken (7) from the Greek word "rhodizein", meaning "to be rose red", which is the color of many of its derivatives, even though rhodizonic acid dihydrate, the form probably involved in analytical work, is colorless. The name is actually more appropriate than earlier workers realized, since anhydrous rhodizonic acid is scarlet red (8). Because of its yellow color, croconic acid was named (4) from the Greek word "krokos", meaning "saffron", a flower of the crocus family. The color called "saffron yellow" is possessed by dried stigmas of this plant.

Although croconates have been studied extensively, they have not found much use as analytical tools. However, it has been shown (34) that Ba^{+2} , Sr^{+2} , and Ca^{+2} may be determined to a sensitivity of $\sim 10^{-3}$ - 10^{-4} M by precipitating the ion with potassium croconate in an ammonium acetate buffer.

On the other hand, rhodizonic acid derivatives have been used to such an extent that rhodizonic acid may be obtained commercially (35), and a review of the analytical uses of sodium rhodizonate has appeared (36). For use in spot test analysis, sodium rhodizonate is recommended (36) for the detection of Ba^{+2} , Sr^{+2} , SO_4^{2-} , and Pb^{+2} in the presence of ions that might otherwise interfere. The test for Pb^{+2} is so sensitive that the lead ion may be detected in very slightly soluble ores, minerals, alloys, pigments, and glasses. Recent applications include: 1) use of barium rhodizonate for the photometric determination of 0.5-0.8 μg . of sulfate in one ml. of solution

(37), and also for the visual determination of sulfate in cross-sections of weathered sedimentary rocks (38); 2) use of potassium rhodizonate for the selective quantitative determination of radiostrontium in biological samples containing large quantities of calcium (39), and also for the determination of 10^{-14} - 10^{-16} M quantities of radio-barium in sea water in the presence of sulfate (40); 3) use of sodium rhodizonate and silver nitrate in the determination of chloride, bromide, and iodide (41); 4) use of rhodizonic acid to separate the rare earth elements into subgroups (42, 43). The order of decreasing tendency to precipitate was found to be $\text{La}^{+3} > \text{Nd}^{+3} > \text{Y}^{+3} > \text{Yb}^{+3} > \text{Cr}^{+3} > \text{Sc}^{+3} > \text{Al}^{+3}$.

Biochemical Applications.--Aromatic oxocarbons have found some biochemical use. Rhodizonic acid stimulates the growth of *Saccharomyces carlsbergensis* in the absence of meso-inositol (44), and also increases the volume of bread from a certain amount of flour (45). Sodium rhodizonate was found to be partially effective in protecting yeast cells against the lethal action of X-rays (46) and ultraviolet light (47), and also was found to reduce the blood pressure in rats who were made hypertensive by wrapping their kidneys in cellophane (48). Croconic acid was found to have a diuretic action on cats (49). Finally, both rhodizonic acid and croconic acid have been shown to enhance the deodorizing action of chlorophyll in the mouth (50). It is added in hard candies, chewing gums, mouth washes, dentifrices, and beverages.

Conclusion.--The field of monocyclic aromatic oxocarbon anions has just been opened (or reopened?). Preliminary experimental results appear to be closely correlated with the results of theoretical calculations. It will be interesting to see whether other members of the $\text{C}_n\text{O}_n^{-m}$ series are stable enough to be synthesized, and also whether their properties will follow the same general trends.

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Note added in proof: The reader is referred to a recent review (51) entitled "Aromatic Anions of the General Formula $C_nO_n^{m-}$ " for an excellent survey of the syntheses of the oxocarbon anions and for a thorough discussion of the structures and properties of their respective acids ($H_2C_nO_n$).

TWO NOVEL UNSATURATED BICYCLIC SYSTEMS

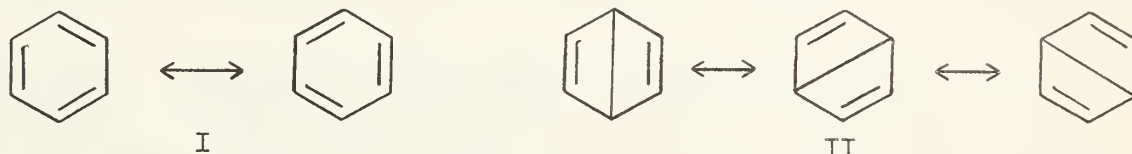
Reported by M. A. Lintner

July 13, 1964

Recently, a great deal of interest has been shown in novel unsaturated bicyclic systems. Two such systems which will be discussed in this seminar are Dewar benzene (bicyclo[2.2.0]hexa-2,5-diene) and barrelene (bicyclo[2.2.2]-2,5,7-octatriene).

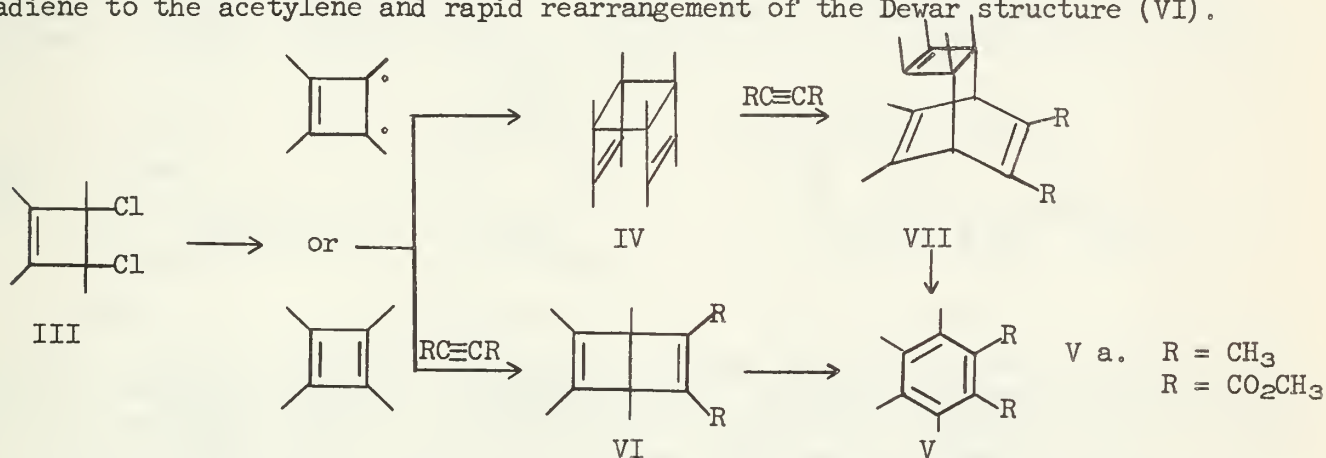
I. Dewar Benzene

In 1865, Kekule (1) proposed the now accepted structure (I) for benzene. The Dewar (2) structure (II) proposed in 1867, was one of a large number of proposals

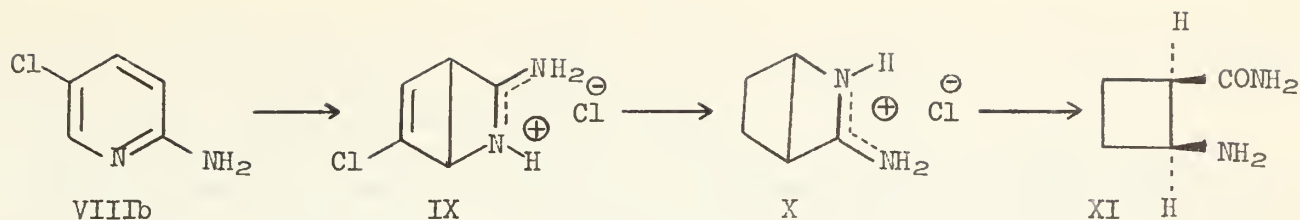


suggested for benzene in the following years. Over the next 60 years, many chemists (3,4,5) seriously considered the Dewar structure as representing benzene. It was only in the 1930's that spectroscopic and theoretical studies led unequivocally to the correct structure of benzene (6,7).

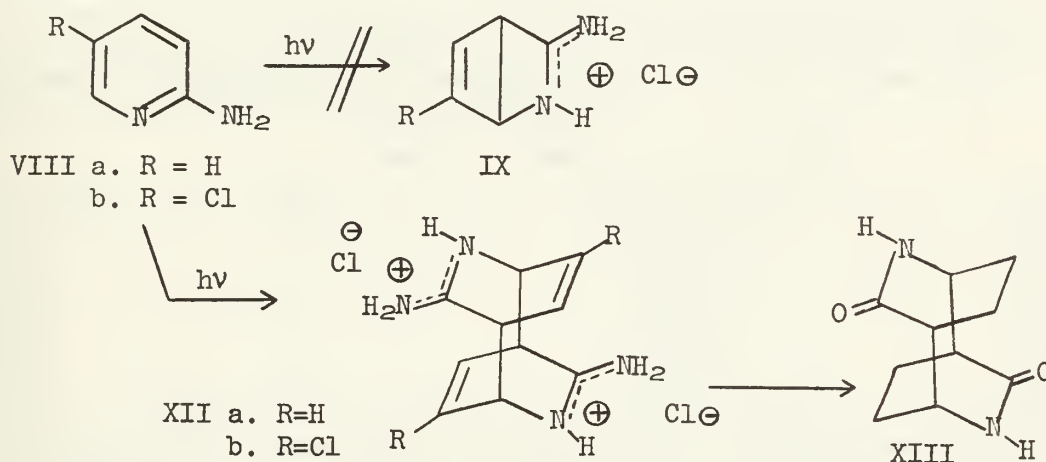
Recently the Dewar representation has been postulated as an intermediate in the synthesis of benzene derivatives (8). Reduction of 3,4-dichloro-1,2,3,4-tetramethyl cyclobutene (III) with lithium amalgam gave the cis-dimer (IV) of tetramethylcyclobutadiene (9). However, when activated zinc dust in 2-butyne was used, hexamethylbenzene (Va) was obtained. Reduction of the dichloride with zinc in dimethyl acetylenedicarboxylate to give dimethyl tetramethyl phthalate (Vb) proved that four atoms of the benzene ring definitely came from the cyclobutene. The cis-dimer was shown to add dimethyl acetylenedicarboxylate to give the Diels-Alder product (VII R=CO₂CH₃) which decomposed on pyrolysis at 330-350° to give the phthalic ester (Vb). The authors contend that the benzene derivatives (V) occur by addition of cyclobutadiene to the acetylene and rapid rearrangement of the Dewar structure (VI).



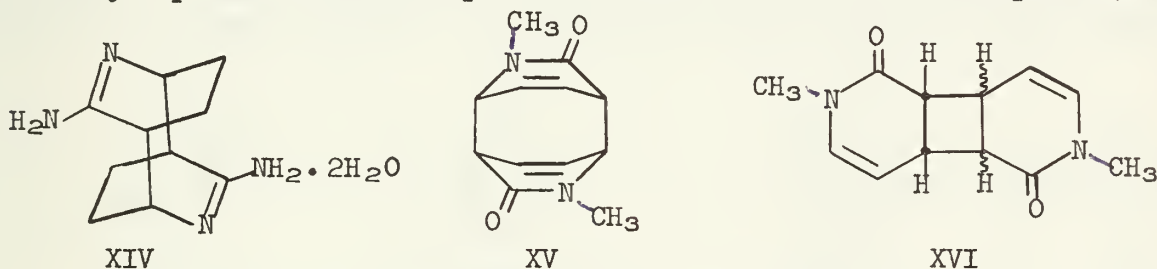
The first reported synthesis of a Dewar benzene-like system was that of a heterocyclic system in which one of the non-bridgehead carbons was replaced by a nitrogen (10). Irradiation of 2-amino-5-chloropyridine (VIIIb) in dilute HCl with sunlight resulted in colorless crystals (IX). The ultraviolet spectrum of the product had only end absorption. When a solution of IX was allowed to stand at room temperature it reverted to VIIIb. The NMR spectrum of IX gave an equal intensity doublet in the vinyl proton region which compared favorably with some values obtained in certain cyclobutenes (11, 12). The spectrum also had peaks consistent with a bridgehead proton in a cyclobutane system adjacent to an electron withdrawing group ($\tau = 5.9, 5.4, 5.2$). Catalytic reduction of IX gave a product (X) which gave cis-2-amino-cyclobutanecarboxamide (XI) upon treatment with 0.1N sodium hydroxide. The following reaction scheme and structures were proposed. Later (13), in the same year, the authors reported the following work to be erroneous and stated that the Dewar compound was not formed and that, instead, the actual product was a dimer (XIIb).



Irradiation of 2-aminopyridine (VIIIa) gave a dimeric product (XIIa) which was converted by hydrogenation and alkaline hydrolysis to a new compound (XIII). This new product was shown to be identical to the tetrahydro derivative of the photodimer of 2-pyridone (14).

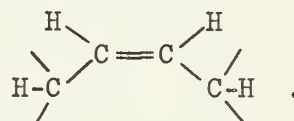


The structure previously assigned to the carboxamide (XI) was proved to be incorrect and structure XIV was shown to be correct (13). Further proof that a dimer was formed was provided by NMR studies of the product of irradiation of N-methyl-2-pyridone (15). NMR analysis showed the dimer to have structure XV and not XVI as previously reported. The NMR spectrum of the dimer has two multiplets ($\tau = 3.35$,



3.77) due to olefinic protons. Examination of these multiplets disclose an AB system (doublet of doublets) with two additional splits. The large asymmetric split ($J = 8$ cps.) indicates cis-olefinic protons (16). The symmetrical second split ($J = 6.5$ cps.) is due to a hydrogen atom α to the double bond (17) having a dihedral angle of about 0 or 180 degrees (18). The third split ($J = 1.5$ cps.) indicates another α -hydrogen coupled through the double bond which suggests the system

The NMR spectrum also shows two peaks due to tertiary hydrogens ($\tau = 5.99, 6.40$) which are also of the AB pattern (16) with two additional symmetrical splits. The large asymmetric split ($J = 9.5$ cps.) is indicative of similar adjacent hydrogens (17) having a dihedral angle of about 0 or 180 degrees. The two symmetrical splits are the counterparts of those described above, and require that all four of the AB type protons be α to the olefinic protons, thus requiring the 1,5-cyclooctadiene structure (XV). The head-to-tail formulation of XV was shown to be correct by dipole moment measurements. Since the assignment of structure XVI to the dimer of N-methyl-2-pyridone was proven to be incorrect, structure IX, which was based, in part, on the comparison of the NMR peaks due to bridgehead protons ($\tau = 5.9$,



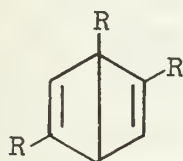
5.4, 5.2) with those for the "cyclobutane" protons of XVI, must be ruled out and replaced by XII. The discovery that structure XIV and not XI was the product of alkaline hydrolysis of the hydrogenation product gave final proof that IX was not the product of irradiation of VIIb and that XII was correct.

The first reported synthesis of a Dewar benzene was that of 1,2,5-tri-*t*-butyl-bicyclo[2.2.0]hexa-2,5-diene by van Tamelen and Pappas (19). van Tamelen stated that "as a non-planar structure, a valence tautomer of the benzenoid system, bicyclo[2.2.0]hexa-2,5-diene should be capable of independent, if precarious, existence." The presence of bulky substituents at positions 1 and 2 would be expected to give steric stabilization to the non-aromatic compound. An ether solution of 1,2,4-tri-*t*-butylbenzene was irradiated to give a new hydrocarbon (XVII) which distilled at 10^{-7} mm. pressure and room temperature. A mass spectrum gave a parent peak at 246 (calculated molecular weight 246), the ultraviolet spectrum showed only end absorption and infrared spectroscopy gave carbon-carbon double bond stretching peaks at 6.26 and 6.46 μ . These peaks are uniquely characteristic of cyclobutene systems (20). The NMR spectrum of XVII showed the following peaks (Table I):

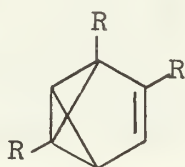
Table I - NMR spectrum of XVII

peak τ value	area	splitting	assignment
3.87	1	singlet	>C=C-H
3.95	1	doublet	>C=C-H
6.80	1	doublet	>C-H
8.94	9	singlet	<i>t</i> -butyl
9.02	18	singlet	<i>t</i> -butyl

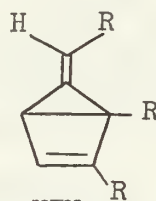
The splitting of the higher field olefinic proton with the methine proton while the lower field olefinic proton remains unsplit gives evidence for two trisubstituted double bonds which implies a bicyclic ring. From the lack of ultraviolet absorption above 220 m μ , it was concluded that the double bonds must be unconjugated. Other than cyclopropene based structures, ruled out by comparison of the chemical shifts of the methine proton in XVII with that reported (21) for cyclopropene systems (τ = 8.6-8.7), four structures (XVII - XX) have been considered and all but XVII involve one or two three-membered rings. Due to inconsistencies with the observed NMR spectrum



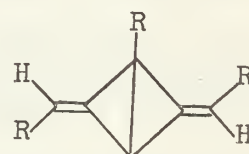
XVII



XVIII



XIX

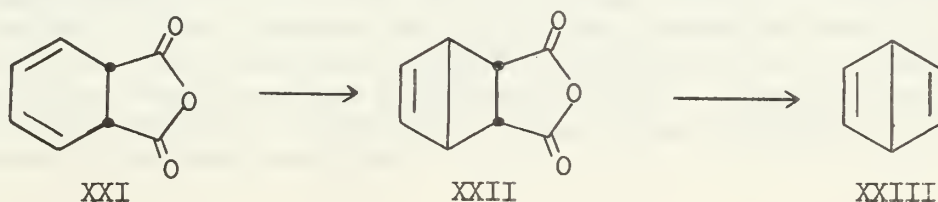


XX

R = *t*-butyl

and the apparent difficulty with which structures XVIII-XX would revert to the benzenoid structure (the product reverted to 1,2,4-tri-*t*-butylbenzene on heating to 200° for 15 minutes), XVII was assigned to the structure of the photoisomer.

In 1963, van Tamelen reported the synthesis of bicyclo[2.2.0]hexa-2,5-diene (Dewar Benzene) (22). Irradiation of an ether solution of *cis*-1,2-dihydrophthalic anhydride (XXI) gave bicyclo[2.2.0]hexa-5-ene-2,3-dicarboxylic acid anhydride (XXII). Treatment of a pyridine solution of XXII with lead tetraacetate gave, after distillation, bicyclo[2.2.0]hexa-2,5-diene (XXIII). The proof of structure was based on the following observations:



1) Heating XXIII in pyridine or allowing its solution to stand for two days gave benzene

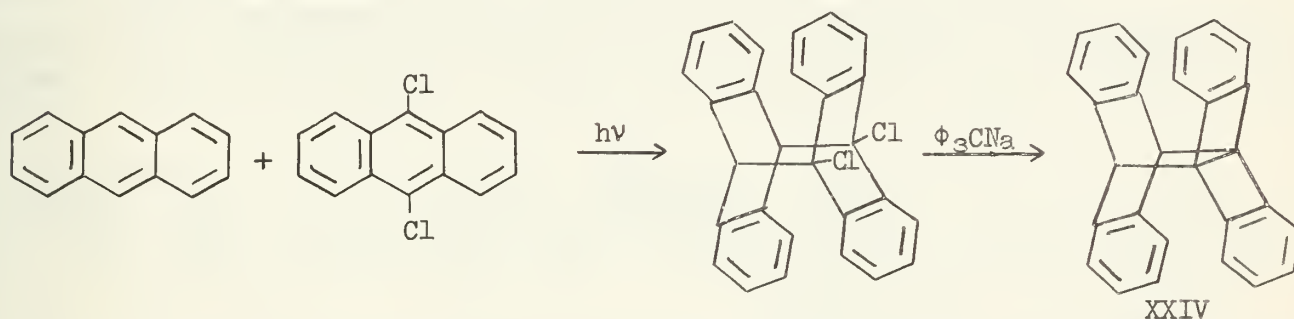
2) The retention time at 45° in VPC (Ucon polar column) is supposedly of the order expected for a C_6 hydrocarbon. For XXIII, 2.7 minutes; for cyclohexene, 3.3 minutes; for bicyclo[2.2.0]hexane, 3.7 minutes; for benzene, 5.7 minutes.

3) Only end absorption was observed in the ultraviolet.

4) The NMR spectrum showed olefinic and methine protons in a two-to-one ratio. The vinyl proton peak was a triplet centered at 3.45τ with splitting due to the two methine protons. Each methine proton was split by all four vinyl protons to give a quintuplet centered at 6.16τ .

5) Reduction of XXIII with diimide gave bicyclo[2.2.0]hexane.

In 1964, Applequist reported the synthesis and structure proof of a "Dewar" anthracene (23). 9,10-dichlorodianthracene, prepared by irradiation of a benzene solution of equimolar amounts of anthracene and 9,10-dichloroanthracene, was treated with triphenylmethylsodium to give 9,10-dehydrodianthracene (XXIV). The product was



allowed to react with bromine to give 9,10-dibromodianthracene which was shown, by infrared spectroscopy, to give a 1:1 mixture of anthracene and 9,10-dibromoanthracene on melting.

Corey (24) has recently done some related work with α -pyrone and N-methyl-2-pyridone. Ultraviolet irradiation of an ether solution of 2-pyrone (XXVa) gave a photoisomer (XXVIa). The structural assignment is based on the following data:

1) Elemental analysis: Calc'd for $C_5H_4O_2$: C, 62.50; H, 4.20; molecular weight, 96. Found: C, 62.37; H, 4.20; molecular weight 96.

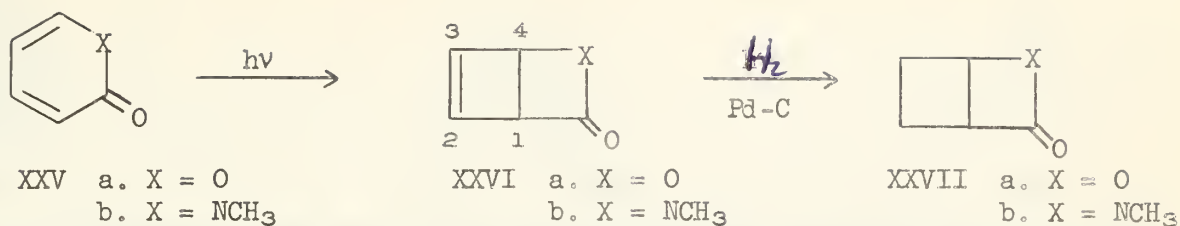
2) The NMR spectrum shows peaks at 3.27τ (octet), 3.42τ (quartet), 4.70τ (quartet) and 5.6τ (octet). The observed chemical shifts support structure XXVIa with the assignments of the above peaks to the protons at C-3, C-2, C-4 and C-1 respectively.

3) The infrared spectrum shows carbonyl absorption as a double peak at 5.41 and $5.5u$ (β lactone) and a band at $6.48u$ due to C=C stretching. The C=C stretching band is at high wavelength due to distortion of bond angles (25).

4) The ultraviolet spectrum shows only end absorption (ϵ 1500 at $210 m\mu$).

Hydrogenation of XXVIa over a palladium-charcoal catalyst proceeds with the uptake of one mole of hydrogen to give a saturated β lactone (XXVIIa) (Calc'd for $C_5H_6O_2$: C, 61.22; H, 6.12. Found: C, 61.26; H, 6.46), having an infrared maximum at $5.5u$ and NMR peaks at 5.2τ (1H), 6.15τ (1H), and 7.57τ (4H).

Photoisomerization of N-methyl-2-pyridone (XXVb) under the same conditions gave XXVIb (Calc'd for C_6H_7NO : C, 66.05; H, 6.42; N, 12.84; molecular weight 109. Found: C, 65.86; H, 6.6; N, 12.92; molecular weight 109). Infrared shows absorption due to β lactam carbonyl at $5.74u$ and C=C stretching at $6.49u$. The NMR shows peaks due to two olefinic protons centered at 3.29τ , two protons attached to saturated carbon at 5.62τ and 5.82τ and three protons of N-CH₃ at 7.18τ . The ultraviolet absorption spectrum shows a maximum at $237 m\mu$ (ϵ 1500). Catalytic reduction of XXVIb produces the saturated lactam (XXVIIb) which shows the NMR and infrared absorptions in agreement with this structure.

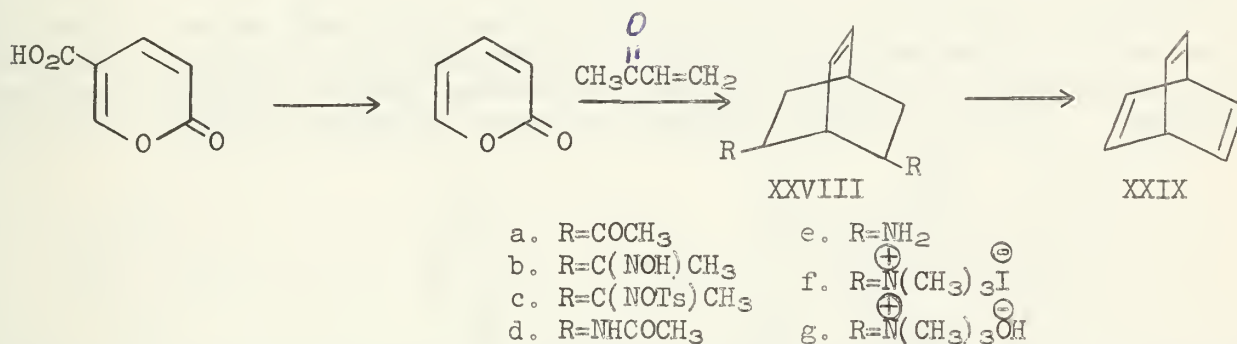


It appears that the solvent has an effect on the irradiation product in that Taylor (13) obtained a dimer in HCl while Corey (24) obtained a photoisomer using ether as the solvent.

II. Barrelene-Bicyclo[2.2.2]-2,5,7-octatriene

Hine (26) was the first to report a study of barrelene. He was interested in determining whether any interaction would exist in the double bonds to give rise to aromatic character, however, he reported no success in its synthesis.

In 1960, Zimmermann (27) reported a successful synthesis of barrelene (XXIX) from α -pyrone-5-carboxylic acid and methyl vinyl ketone according to the following reaction scheme. α -pyrone-5-carboxylic acid was decarboxylated over copper at 650°. A decar-

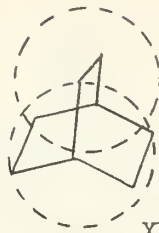


boxylative double diene synthesis was accomplished by heating α -pyrone with excess methyl vinyl ketone to give 5,7-diacetylbicyclo-[2.2.2]-2-octene (XXVIIIa). The dioxime (XXVIIIb) was prepared and converted to the di-*p*-toluenesulfonate (XXVIIIc). Solvolytic Beckmann rearrangement gave the amide (XXVIIId) which was hydrolyzed to give the amine (XXVIIIe). The amine was converted to the dimethiodide (XXVIIIf) which was converted to the dimethoxyhydroxide (XXVIIIg). Pyrolysis of the dimethoxyhydroxide at 90-110° gave an oil which, after V.P.C., afforded barrelene (XXIX). Barrelene exhibits infrared absorption, due to carbon-carbon double bond stretching, at 6.2 μ and ultraviolet absorption at 208m μ (log ϵ 3.05) and 239m μ (log ϵ 2.48). The NMR spectrum showed a quartet, due to vinyl protons, centered at 3.36 τ and a multiplet, due to bridgehead protons centered at 5.31 τ , having relative area 2.95:1. Barrelene, which is stable at 200°, is converted into benzene and acetylene at 250°. Hydrogenation of barrelene gave bicyclo[2.2.2]octane.

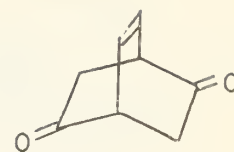
Simple LCAO-MO calculations indicate that if 2,6 overlap were as effective as 2,3 overlap then barrelene would have the same delocalization energy as benzene. However, Zimmermann states that his calculations - the basis for which is not discussed - suggest only 22.5% as much overlap, which leads him to the prediction that barrelene should have no delocalization energy, even though the six π electrons appear in three delocalized orbitals (degenerate pair at 1.225 β and one at 0.55 β). "Barrelene is subject to electron delocalization without the usually coexisting delocalization energy." Zimmermann derives the name from the barrel shape of the π electron cloud (XXX). Zimmermann (29) states that Tedder (28) has erroneously interpreted the above to indicate that he has claimed that the π electrons coalesce (XXXI). Tedder (28) says that he can see no reason why XXIX should be named barrelene and cites the fact that bicyclo[2.2.2]oct-7-ene-2,5-dione (XXXII) has been synthesized (30) and shows no tendency to enolize, thus providing a strong argument against structures of type XXXI.



XXX

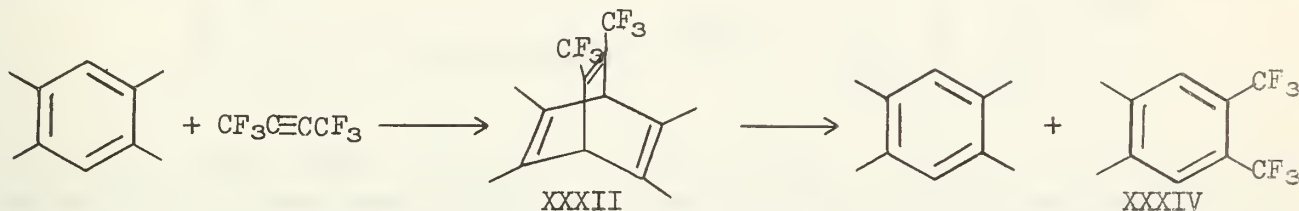


XXXI

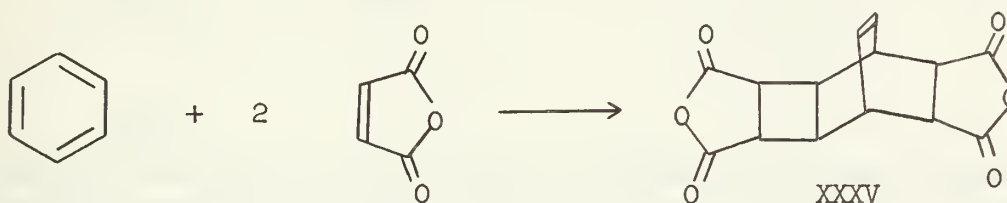


XXXII

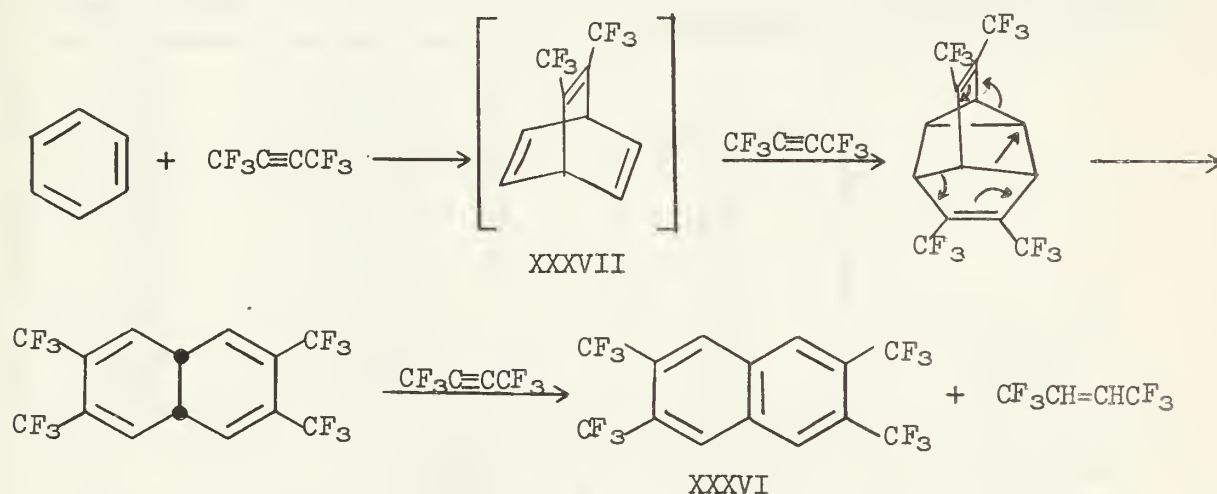
Barrelene derivatives were synthesized and utilized as intermediates by Krespan, McKusick and Cairns (31, 32). 2,3,5,6-tetramethyl-7,8-bis-(trifluoromethyl)-bicyclo-[2.2.2]-octa-2,5,7-triene (XXXIII) was synthesized from durene and hexafluoro-2-butyne. Pyrolysis of XXXIII at 250° gave durene and 1,2-dimethyl-4,5-bis-(trifluoromethyl)-benzene (XXXIV).



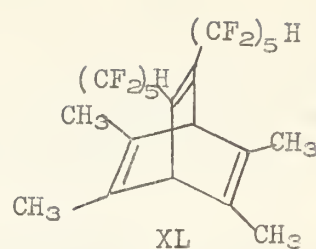
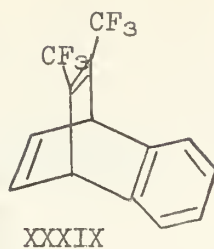
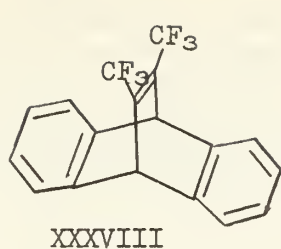
The authors stated that this reaction was believed to be the first example of a simple Diels-Alder reaction utilizing the ring of a simple benzene derivative as the diene. They were incorrect in their assumption since, in 1959, benzene was shown to add two molecules of maleic anhydride to give the diadduct (XXXV) (33,34,35). Heating a



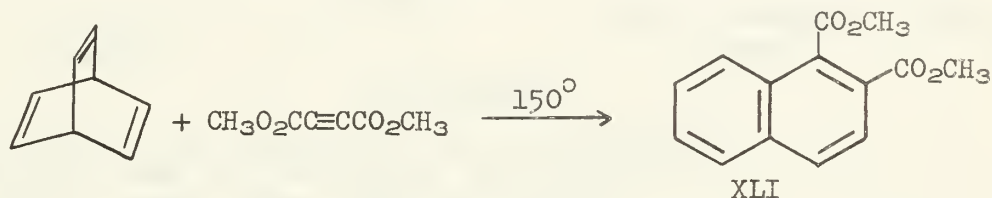
mixture of hexafluoro-2-butyne and excess benzene gave principally 2,3,6,7-tetrakis-(trifluoromethyl)-naphthalene (XXXVI). The mechanism is believed to proceed via the bicyclooctatriene (XXXVII) as illustrated below.



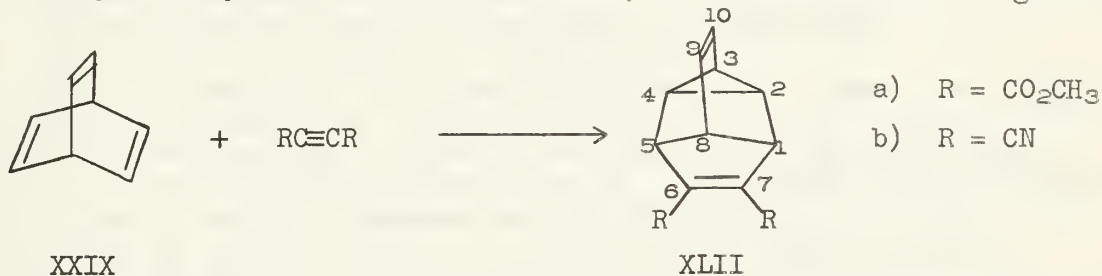
Hexafluoro-2-butyne has also been shown to add to anthracene to give the expected Diels-Alder product 9,10-[1,2-bis-(trifluoromethyl)-etheno]-9,10-dihydroanthracene (XXXVIII) and to naphthalene to give 1,4-etheno-2,3-bis-(trifluoromethyl)-1,4-dihydronaphthalene (XXXIX). In addition, durene was shown to react with 1,12-dihydro-eicosafuoro-6-dodecyne to give 2,3,5,6-tetramethyl-7,8-bis-(5-hydrodecafluoropentyl)-bicyclo[2.2.2]octa-2,5,7-triene (XL). No products were obtained on reaction of durene with acetylene or 1,1,1-trifluoropropyne.



Zimmermann (29,38) has studied the conversion of barrelene to naphthalene derivatives. Barrelene reacts with dimethyl acetylenedicarboxylate at 150° to give dimethyl naphthalene-1,2-dicarboxylate (XLI). In order to elucidate the mechanism of this re-



action, lower temperatures were used. At 100°, dimethyl acetylenedicarboxylate gave a monoadduct with barrelene (XLIIa) and a similar adduct (XLIIb) resulted from the reaction of dicyanoacetylene with barrelene at 25°. The structural assignments for



these adducts were supported by elemental analysis, NMR spectra (Table II), analogy with the dicyanoacetylene adduct of norbornadiene (36,37) and are consistent with the observed ultraviolet spectra (Table III).

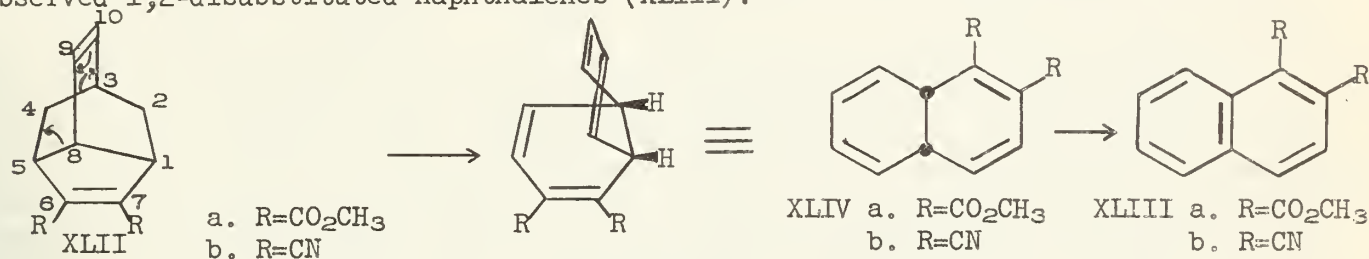
Table II - NMR Data

Adduct	Peak τ value	splitting	area	positional assignment	corresponding peak norbornadiene adduct ³⁷
XLIIa	3.47	triplet	1	9	
	4.14	triplet	1	10	
	6.20	singlet	6	methoxyls	
	7.2-7.6	multiplet	2	3,8	
	7.67	singlet	2	1,5	
XLIIb	8.19	doublet	2	2,4	
	3.37	triplet	1	9	
	4.10	triplet	1	10	
	7.0-7.5	multiplet	2	3,8	7.95, 7.55
	7.59	singlet	2	1,5	6.96
	8.13	doublet	2	2,4	8.22

Table III - Ultraviolet Data

Compound	$\lambda_{\text{max}}^{\text{EtOH}}$	log ϵ	reference
XLIIa	245	3.84	29
XLIIb	251	3.94	29
	285	3.58	29
Norbornadiene-dicyanoacetylene adduct	255	3.90	36

These adducts were converted to 1,2-disubstituted naphthalenes (XLII) on heating. The authors contend that the mechanism of the conversion of adduct (XLII) to naphthalene involves a low energy transformation in which bonds 3-4 and 5-8 (or 1-8 and 2-3) break in a concerted process to give a 4-5 (or 1-2) π bond and a diene moiety comprising atoms 3,8,9 and 10. The resulting 9,10-dihydro-1,2-disubstituted naphthalene (XLIV) is believed to undergo intermolecular hydrogen transfer to give the observed 1,2-disubstituted naphthalenes (XLIII).



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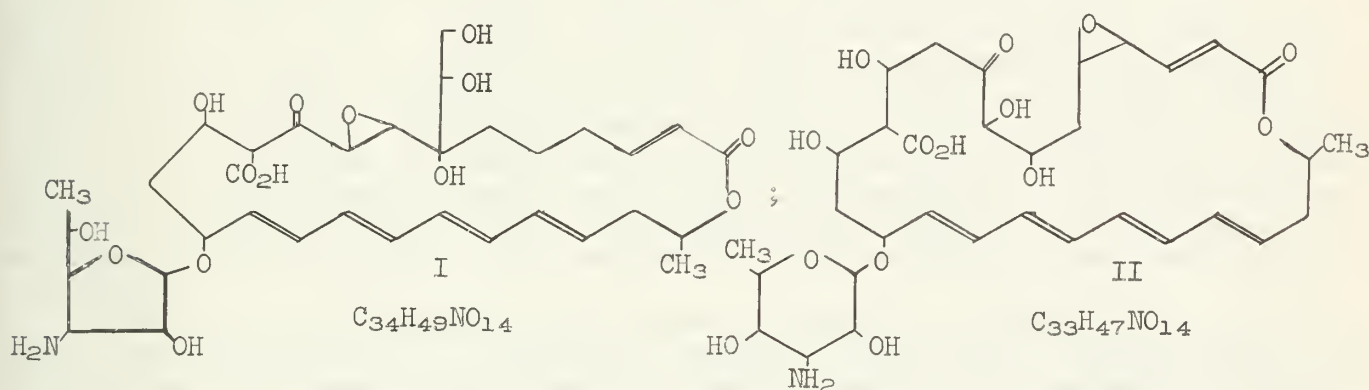
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THE STRUCTURE OF PIMARICIN

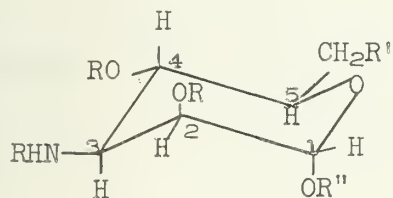
Reported by Ping Huang

July 15, 1964

Introduction.--Pimaricin ($C_{33}H_{47}NO_{16}$) a crystalline antifungal antibiotics was isolated from the fermentation broth of a culture of *Streptomyces* species, obtained from a soil sample of the Union of South Africa. Its isolation and properties were first described by Hoogerheide et al (1). Pimaricin is a very stable crystalline compound without a definite melting point but decomposing gradually at approximately $200^{\circ}C$. The early studies (2) showed that pimaricin contained an α,β -unsaturated lactone grouping, a carboxyl group, a ketone and a primary amine. The antibiotic also has six hydroxyl groups and contained five double bonds, but on reduction gave a dodecahydro compound which contained an addition hydroxyl group. This indicated the presence of an epoxide function. Pimaricin has a very strong absorption in the ultraviolet with maxima at 279, 290, 303 and 318 $m\mu$. The intensity and spacing of the absorption bands are characteristic of an all-trans unsubstituted conjugated tetraene system. Hydrolysis of pimaricin with strong acid in methanol gave the methyl glycoside of mycosamine (3), an amino-hexose previously isolated from several other antifungal antibiotics including nystatin (4), and amphotericin B (5). Pimaricin was the first polyene antibiotics chemically investigated, and in 1958, Patrick et al (2) proposed the structure (I). An attempt to rationalize this carbon skeleton and oxygenation pattern in terms of an acetate biogenesis was not successful. On the basis of new chemical evidence, the structure (II) for pimaricin was proposed by Ceder (6) in 1964. This seminar will present mainly the data supporting the new structure.



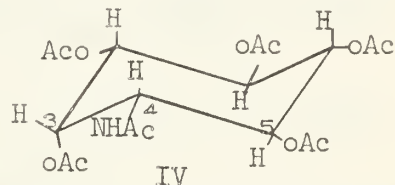
Configuration of Mycosamine (7).--As stated above, hydrolysis of pimaricin with strong acid in methanol gave the methyl glycoside of mycosamine (IIIa). Degradation with periodate had previously shown that mycosamine is a 3,6-dideoxy-3-amino-hexose (8). More recently, Wintersteiner and coworkers reported its synthesis and absolute configuration (9,10). The nuclear magnetic resonance spectrum of the mycosamine tetraacetate (IIIb), obtained by treatment of pimaricin with acetic anhydride and sulfuric acid (8), showed a three protons doublet at $\delta = 1.20$ ($J=6$ cps) due to C-5 methyl group. The proton on C-5 appeared as a quartet, centered at $\delta = 3.98$ ($J=6$ cps) and was further split to an octet by C-4 proton ($J=8.5$ cps). The splitting indicated probably an axial-axial relationship between H-4 and H-5 (11). The twelve acetyl protons appeared as three singlets at $\delta = 2.18$, 2.09 and 1.93 with the ratio of 2:1:1. It is known that axial acetyl groups have higher δ values than equatorial ones (12,13), the six protons at $\delta = 2.18$ represented two axial acetyl groups on C-1 and C-2. When the spectrum of (IIIb) was recorded in the presence of a small amount of trifluoroacetic acid, the band at $\delta = 1.93$ moved to $\delta = 2.05$, while the other two singlets remained unchanged. It was believed the shift was caused by weak protonation of the amide nitrogen. The band



- III a $R=R'=H$, $R''=CH_3$
 b $R'=H$, $R=R''=CH_3CO$
 c $R=H$, $R'=OH$, $R''=CH_3$

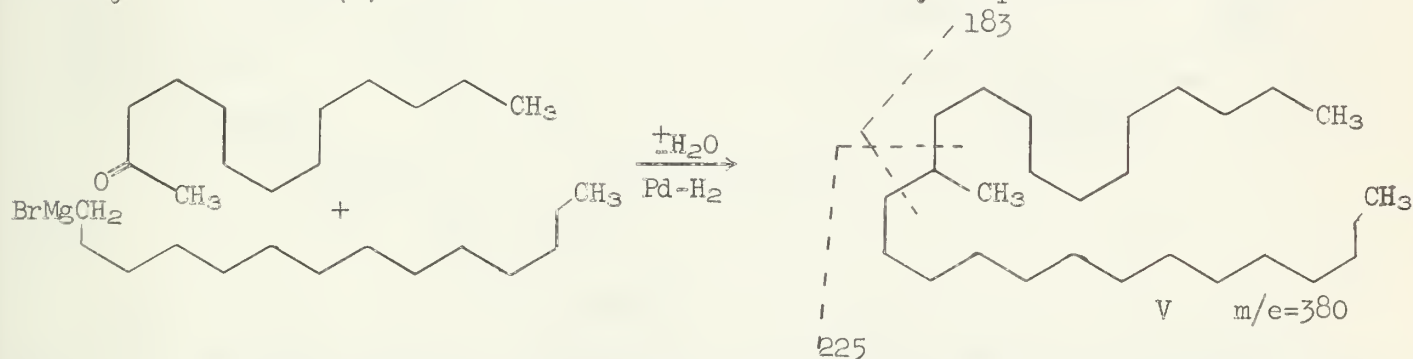
acetyl groups have higher δ values than equatorial ones (12,13), the six protons at $\delta = 2.18$ represented two axial acetyl groups on C-1 and C-2. When the spectrum of (IIIb) was recorded in the presence of a small amount of trifluoroacetic acid, the band at $\delta = 1.93$ moved to $\delta = 2.05$, while the other two singlets remained unchanged. It was believed the shift was caused by weak protonation of the amide nitrogen. The band

at $\delta=2.09$ was then due to the acetyl group at C-4 which was equatorial. At $\delta=6.01$, there were two protons in form of two overlapping doublets. In the presence of trifluoroacetic acid, one proton remained unchanged and the other moved to $\delta=6.65$. The remained doublet at $\delta=6.01$ ($J=1.5$ cps) represented the anomeric proton (13,14), the coupling constant indicated an equatorial-equatorial relationship between H-1 and H-2. The other doublet ($J=8$ cps) was due to the amide proton which was split by H-3. The remaining three protons at C-2, C-3 and C-4 appeared as ABC pattern between $\delta=4.5$ and 5.1. Hexaacetyl-DL-mysinosamine (IV) has by chemical methods been shown to have an equatorial-axial relationship among H-3, H-4, and H-5 (15). The splitting pattern for those protons was virtually identical with that of the corresponding protons in (IIIb). This fact also supported the amino group in mycosamine was equatorial (10). Mycosamine has been prepared from the sugar (IIIc) (16), which in turn has been converted from glucose (17).



The Carbon Skeleton of Pimaricin.—Hydrogenation of pimaricin in the presence of platinum followed by reduction with lithium aluminum hydride yielded a noncrystalline polycol. Treatment of the polycol with red phosphorus and concentrated hydriodic acid and then with lithium aluminum hydride followed by catalytic reduction (18) produced an oil with infrared spectrum characteristic of a saturated hydrocarbon. Gas chromatography indicated it was a mixture of two very similar compounds. The mass spectrum showed two molecular ion peaks at $m/e=380$ and 366 which corresponded to the molecular formulas $C_{27}H_{56}$ and $C_{26}H_{54}$. Reductions with hydriodic acid are known to cause rearrangements and cleavage of carbon-carbon bonds. Therefore, the basic skeleton of pimaricin probably contained twenty-seven carbon atoms. To verify this, a milder degradation was tried (19). Catalytic reduction of pimaricin followed by sodium borohydride treatment gave a polyhydroxy lactone. This on dehydration with phosphorus oxychloride followed by catalytic hydrogenation and reduction with lithium aluminum hydride gave a polycol. The polycol was then treated with red phosphorus and iodine (20), and the resulting polyiodide was converted to a saturated hydrocarbon by treatment with lithium aluminum hydride and catalytic hydrogenation. The hydrocarbon was shown by mass spectrometry to have a molecular weight of 380 which corresponded to a molecular formula of $C_{27}H_{56}$. The mass spectrum also exhibited strong peaks at $m/e=183$ and 225.

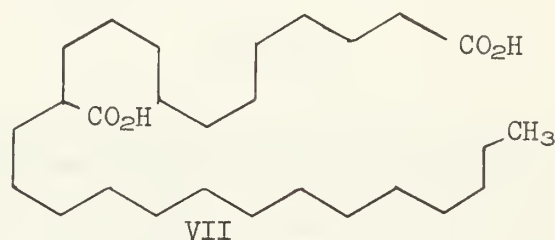
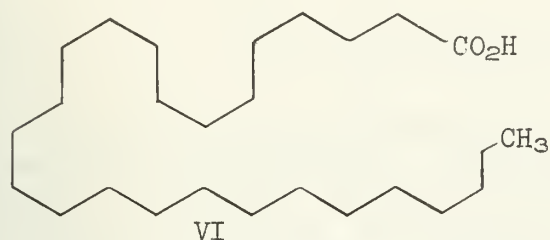
Oxidation of the heptacosane with chromic anhydride in glacial acetic acid (21) gave a steam volatile acid, identified as dodecanoic acid by gas chromatography of the methyl ester. The mass spectrum and the oxidation results were compatible only with 12-methyl-hexacosane (V). This structure was confirmed by comparison with an authentic



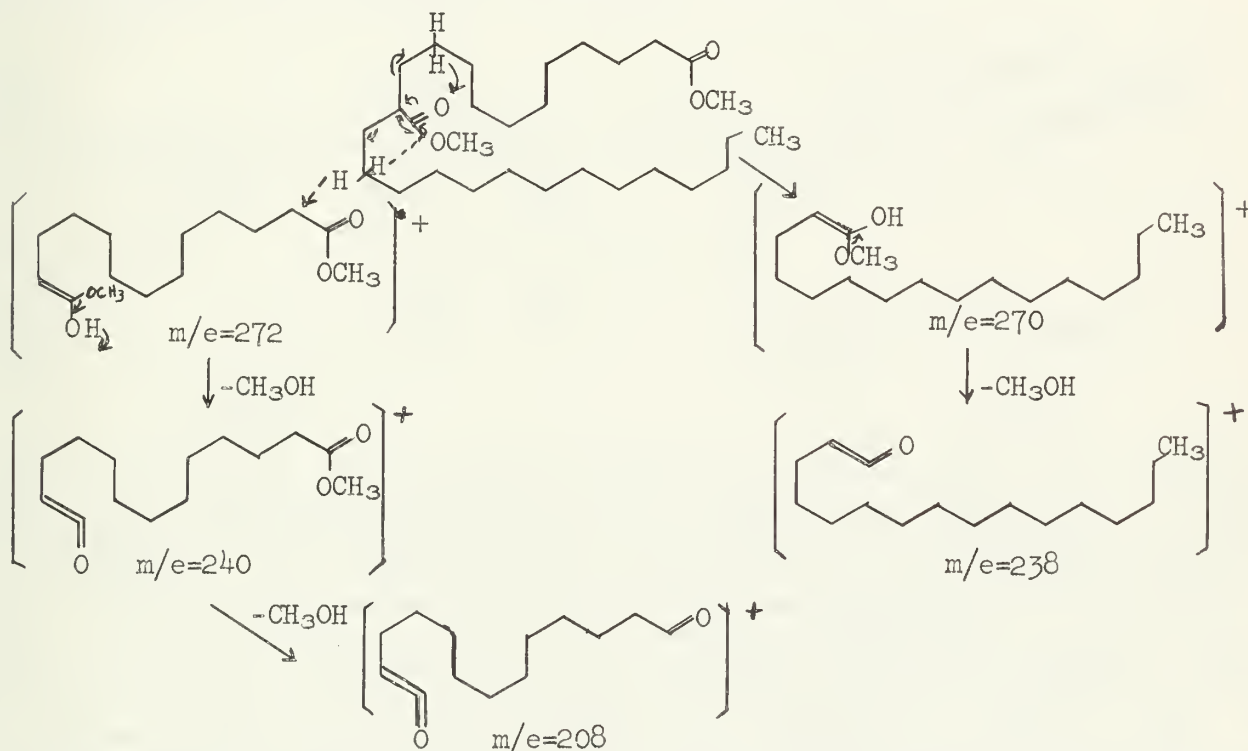
sample synthesized from myristyl bromide and tridecanone-2. If pimaricin had the structure (I), the hydrocarbon obtained through the same series of reactions would have been 11-methyl-7-ethyl-pentacosane. Thus structure (I) is untenable and the antibiotic has the skeleton (V).

Degradation Products from High Pressure, High Temperature Treatment.—Catalytic hydrogenation of pimaricin at 250° - 300° and 200 atm. yielded four crystalline compounds (VI), (VII), (VIII), and (IX) (22). (VI) was a saturated compound without any high-intensity ultraviolet absorption. The infrared spectrum of (VI) (714 , 1695 cm^{-1} and

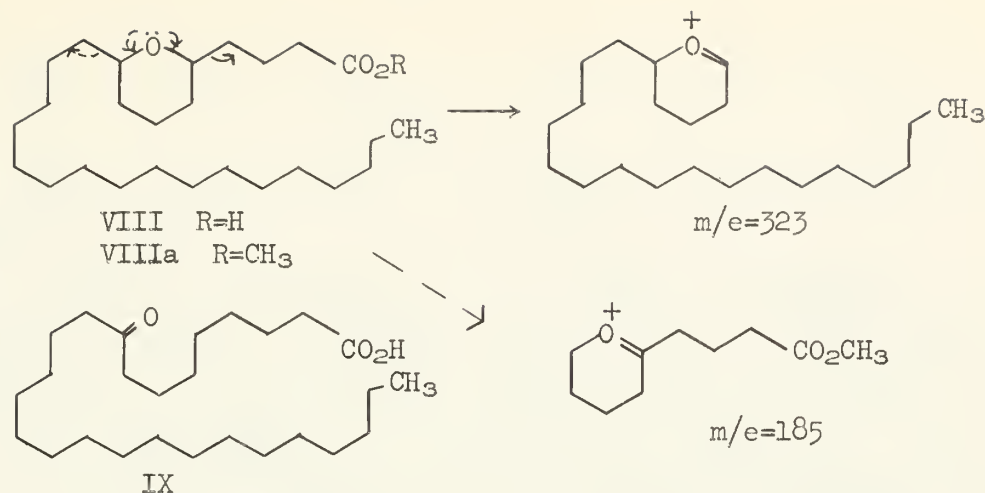
broad absorption between 2400-3500 cm^{-1}) indicated it was a fatty acid. The mass spectrum of the methyl ester of (VI) showed a molecular weight of 410, corresponding to $\text{C}_{25}\text{H}_{51}\text{CO}_2\text{CH}_3$ and was identical with that of authentic hexacosanoic acid methyl ester. (VII) was also a saturated compound. The infrared spectrum was very similar to that of (VI). (VII) was shown to be a dibasic acid by electrometric titrations. Treatment of the methyl ester with lithium aluminum hydride followed by red phosphorus and iodine and again with lithium aluminum hydride reduced (VII) to a saturated hydrocarbon, which was identical with the synthetic 12-methyl-hexacosane (V). Oxidation of (VII) with potassium permanganate in acetone (23) gave a mixture of acids. Gas chromatographic analysis of the methyl esters showed pentadecanoic acid was the highest monobasic acid formed. (VII) was then assigned to be 2-tetradecyltridecandioic acid.



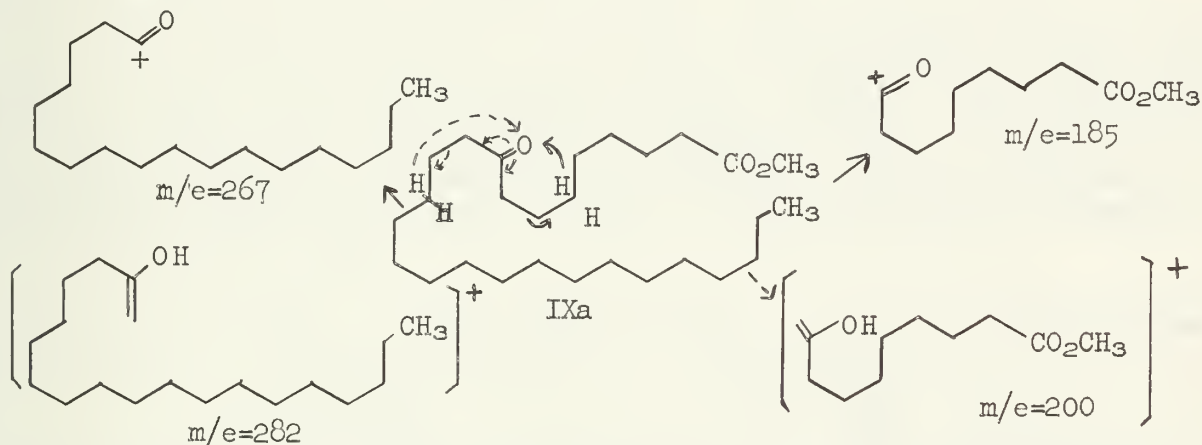
Additional evidence for (VII) was obtained from the mass spectrum of the methyl ester. The molecular ion peak at $m/e=468$ corresponding to the compound $\text{C}_{29}\text{H}_{59}\text{O}_4$, and two most intense peaks appeared at $m/e=272$ and 270. They were formed through a rearrangement as indicated below (24). The correctness of these assignments was supported by the appearance of the fragments with $m/e=240$, 238 and 208.



(VIII) was also a long chain fatty acid with infrared bands at 715, 1080 and 1688 cm^{-1} . The nuclear magnetic resonance spectrum of the methyl ester showed a broad band at $\delta=3.18$ (2 H) indicating the presence of a cyclic ether. Oxidation of (VIII) with chromium trioxide in acetic acid gave a mixture of acids. The highest volatile acid was found by gas chromatography of the methyl esters to be octadecanoic acid, and the nonvolatile dibasic acids consisted of a mixture of approximately equal amounts of succinic acid and glutaric acid. These results suggested (VIII) to be 5,9-epoxy-hexacosanoic acid. The mass spectrum of the methyl ester (VIIIa) showed a molecular ion peak at $m/e=424$ and two peaks at $m/e=323$ and 185 which were formed by loss one or other of the chains attached to the tetrahydropyran ring.

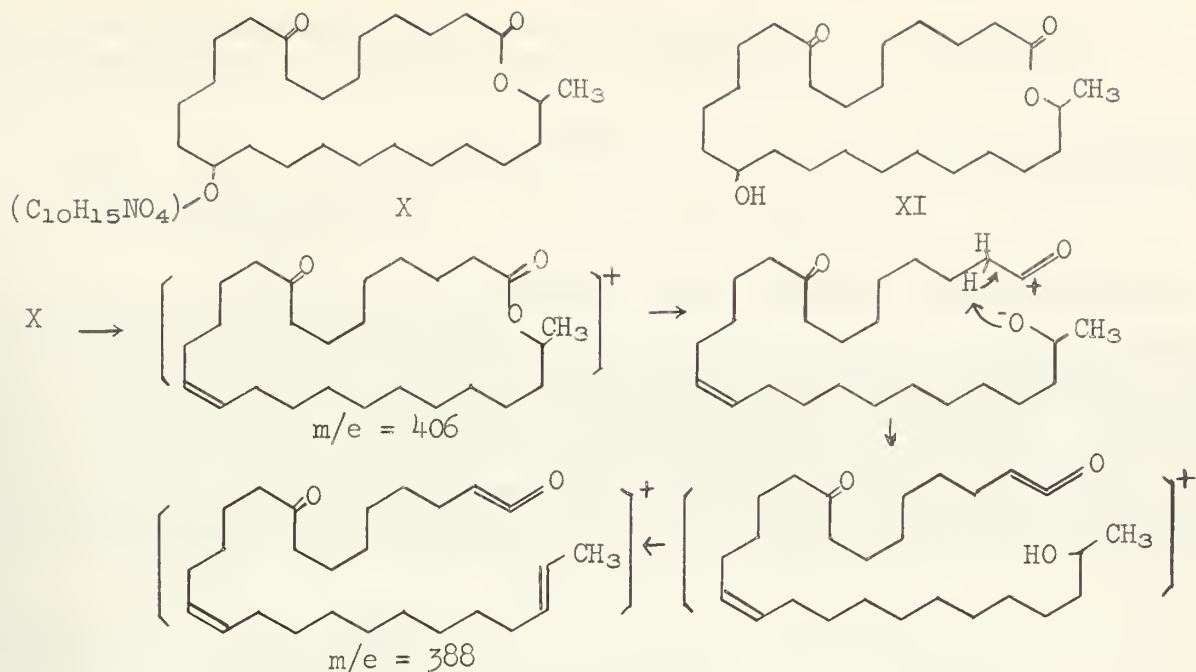


(IX) was a long chain fatty acid with infrared bands at 712, 1412, 1693 cm^{-1} and broad band at 2500-3500 cm^{-1} . The infrared spectrum of the methyl ester showed the presence of the ester (1736 cm^{-1}) and a ketone group (1708 cm^{-1}). Additional evidence for the carbonyl groups was obtained from the nuclear magnetic resonance spectrum with a multiplet at $\delta=2.1$ (6H). Oxidation of (IX) with chromium trioxide in acetic acid gave a mixture of acids. Gas chromatography of the methyl esters showed octadecanoic acid to be the highest monobasic acid. (IX) was assigned the structure 9-oxohexacosanoic acid. The structure was confirmed by the mass spectrum of the methyl ester (IXa) which gave fragments at 282, 267, 200 and 185.

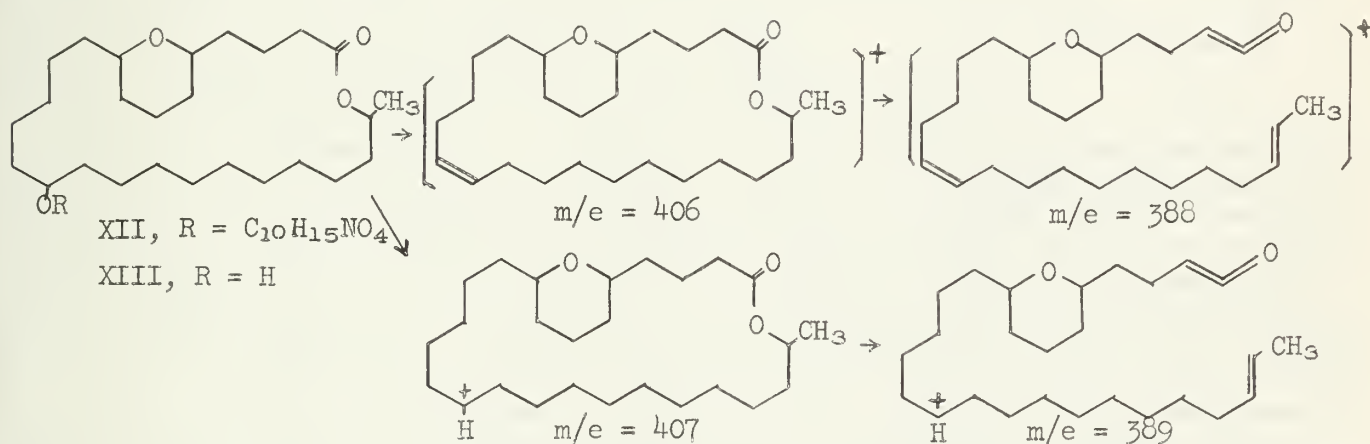


When pimarinin was catalytically hydrogenated in glacial acetic acid at 150° and 150 atm., two new crystalline compounds, (X) and (XII) were obtained (25). (X) has a molecular weight of 637, determined by mass spectrometry and corresponded to $\text{C}_{33}\text{H}_{63}\text{NO}_8$ with microanalysis. The infrared spectrum showed bands at 1418, 1710 and 1725 cm^{-1} . Reduction of (X) with potassium borohydride caused the disappearance of the band at 1710 cm^{-1} . These results indicated a lactone structure containing a ketone group. Treatment of (X) with hydriodic acid and red phosphorus followed by catalytic reduction gave 9-oxohexacosanoic acid which was identical with an authentic sample. A new compound (XI) was obtained by treating (X) with dilute hydrochloric acid in acetone. Mass spectrometry showed its molecular weight to be 424, corresponding to $\text{C}_{26}\text{H}_{48}\text{O}_4$ with microanalysis. Infrared absorption at 1704 cm^{-1} and 1724 cm^{-1} indicated the presence of a ketone group and a lactone group as in (X). Oxidation of (XI) with chromium trioxide in acetic acid gave a mixture of dibasic acid. Gas chromatography of the methyl esters revealed that undecandioic acid was the highest one formed. The nuclear magnetic resonance spectrum showed a three protons doublet at $\delta=1.20$ ($J=6$ cps) and one proton quartet with fine structure at $\delta=4.95$ which is typical of a α -methyl lactone structure (26).

The mass spectrum of (XI) was virtually identical with the lower region of that of (X) except for small intensity difference. Two characteristic fragments at $m/e=406$ and 388 indicated the loss of two water from (X).

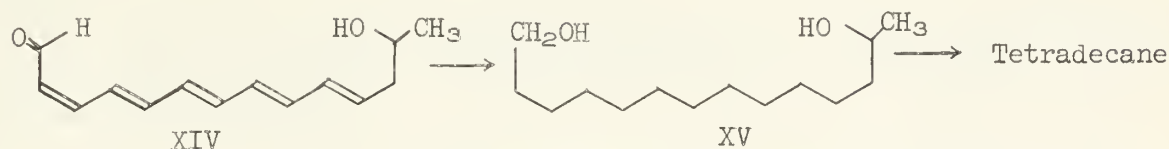


The second crystalline compound (XII) has the same molecular weight and analytical data as (X). The infrared spectrum showed only a sharp band 1725 cm^{-1} in the 6μ region. No ketonic groups were present in (XII) and as it was a saturated isomer of (X), it should contain one additional cyclic ether ring. This was supported by the presence of a broad four protons signal at $\delta = 3.3$ in the nuclear magnetic resonance spectrum of (XII), the same region in (X) contained only two protons. Oxidation of (XII) with chromium trioxide in acetic acid produced a number of dibasic acids of which undecandioic acid was the highest one obtained. Hydrolysis of (XII) in acetone with dilute hydrochloric acid yielded a new compound (XIII). The mass spectrum showed the molecular weight was 424, like (XI), it lost two moles of water and gave four fragments at $m/e = 406$, 407, 388 and 399.



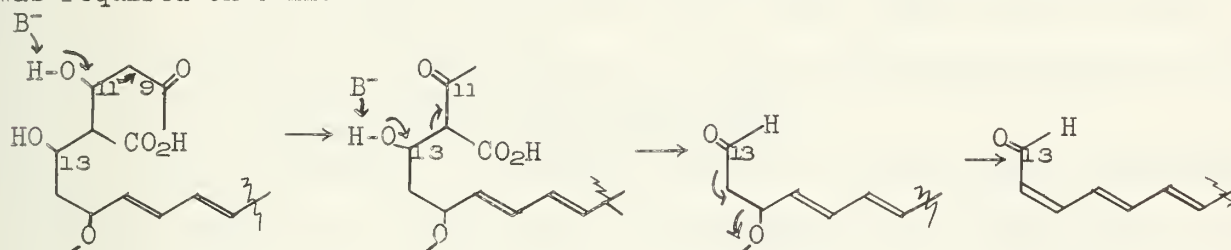
Pattern of Unsaturation.—The infrared spectrum of pimaricin showed a band at 1712 cm^{-1} which shifted to 1733 cm^{-1} on hydrogenation. The ultraviolet spectrum showed a maximum at $222m\mu$ ($\epsilon = 22,400$) which disappeared on hydrogenation. These results indicated the presence of a α,β -unsaturated lactone (2). The ultraviolet maxima at 279, 290, 303 and $318m\mu$ indicated the presence of an all-trans unsubstituted, conjugated tetraene (4,27). Treatment of pimaricin with 5% aqueous sodium hydroxide gave the conjugated pentaene aldehyde (XIV) (2,25) with strong ultraviolet absorption at $378m\mu$ (28). Its infrared spectrum showed it contained hydroxyl and aldehyde group (3500 , 2850 and 2750 cm^{-1}) and conjugated carbonyl group (1690 cm^{-1}). Catalytic hydrogenation of (XIV) followed by reduction with sodium borohydride gave the saturated diol (XV) which was converted to a saturated hydrocarbon through red phosphorus and

iodine followed by treatment with lithium aluminum hydride. The hydrocarbon was shown by gas chromatography and mass spectrum to be identical with tetradecane.

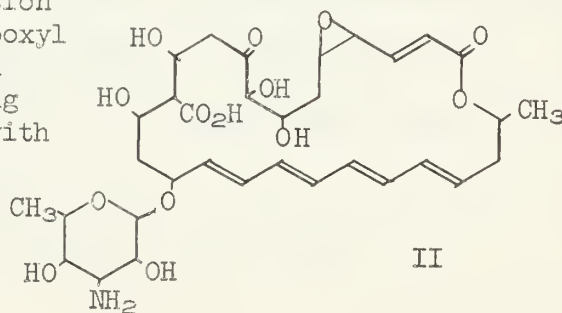
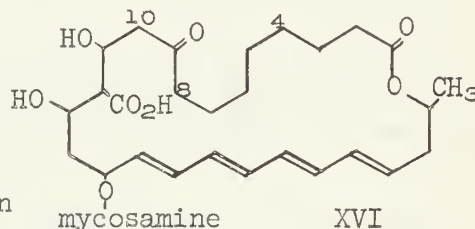


Ozonolysis of (XIV) gave crotonaldehyde which confirmed (XIV) as 13-hydroxy-2,4,6,8,10-tetradodecapentaene-1-al.

The pentaene aldehyde was formed under conditions inducing retroaldol reactions. Therefore, C-13 in pimaricin carried a hydroxyl group and the cleavage of the bond between C-12 and C-13 was triggered by a carbonyl group at β -position. If pimaricin was reduced with sodium borohydride before treatment with sodium hydroxide, no (XIV) could be detected. This result indicated that the C-9 ketone groups was the origin of the retroaldol reaction which proceeded in two steps and consequently a hydroxyl group was required on C-11.



The Complete Structure of Pimaricin.--The preceding evidence demonstrated that pimaricin has the partial structure (XVI). As the antibiotic has the empirical formula $C_{34}H_{47-49}NO_{14}$ (27), three oxygen remained to be placed. Pimaricin did not yield any saturated dicarboxylic acid on vigorous oxidation, and so it probably does not contain two or more adjacent methylene group in the chain. Treatment of ethylene oxides adjacent to a carbonyl group with potassium iodide and acetic acid is known to remove the oxygen atom and introduce a double bond (29). This reaction was used to prove the presence of an epoxide function in the macrolide magnamycin (30). Treatment of pimaricin with the same reagent gave a product which had strong ultraviolet maximum at 269 m μ ($\epsilon = 27,000$) (difference spectrum) indicating a $\alpha\beta, \gamma\delta$ -conjugated carbonyl system. The epoxide function was then assigned to the carbons adjacent to the $\alpha\beta$ -unsaturated lactone. The nuclear magnetic resonance spectra of the N-acetyl derivatives of pimaricin and dodecahydropimaricin showed methine protons at $\delta = 3.00$ (31) and 3.38 providing additional evidence for the presence of the epoxide ring. Reductive opening of the epoxide created a new hydroxyl on C-5 which formed a hemiacetal with the ketone group on C-9 and thus explained the presence of a 5,9-epoxy ring system in (VI) and (XI). N-acetylpimaricin and N-acetyldodecahydropimaricin each consumed two equivalents of periodate in neutral medium. A hydroxyl group on C-6 did not accord with the finding. C-10 was believed to be unsubstituted because a hydroxyl group in this position would be able to form a γ -lactone with the carboxyl group on C-12. These results indicated C-7 and C-8 as the only possible sites for the remaining hydroxyl groups. The arrangement agreed well with the observations that one mole of periodate was consumed immediately and the second one after two hours (2) and that after completion of the oxidation, the solution was acidic. Further support for the assumption was obtained from the fact that periodate-permanganate oxidation (32) of N-acetyldodecahydropimaricin



followed by basic hydrolysis in no case yielded a saturated hydroxyl free dibasic acid. The complete structure of pimaricin was therefore (II).

Conclusion.—Chemical evidence leading to the complete structure of pimaricin has been presented. The variation of reaction conditions of the high temperature high pressure hydrogenation, followed by careful investigation of the products might form the basis of a general method for determining the structures of complex polyhydroxy polyene macrocyclic antibiotics.

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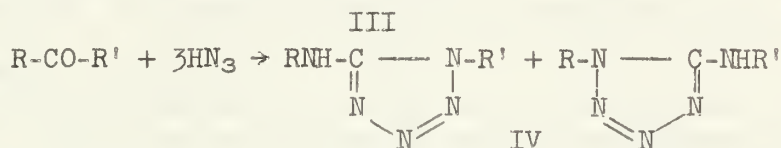
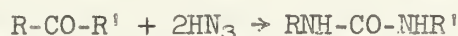
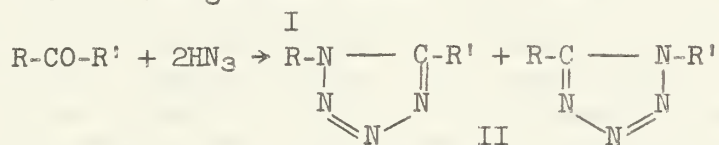
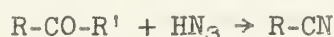
THE SCHMIDT REACTION WITH KETONES

Reported by Allan C. Buchholz

July 20, 1964

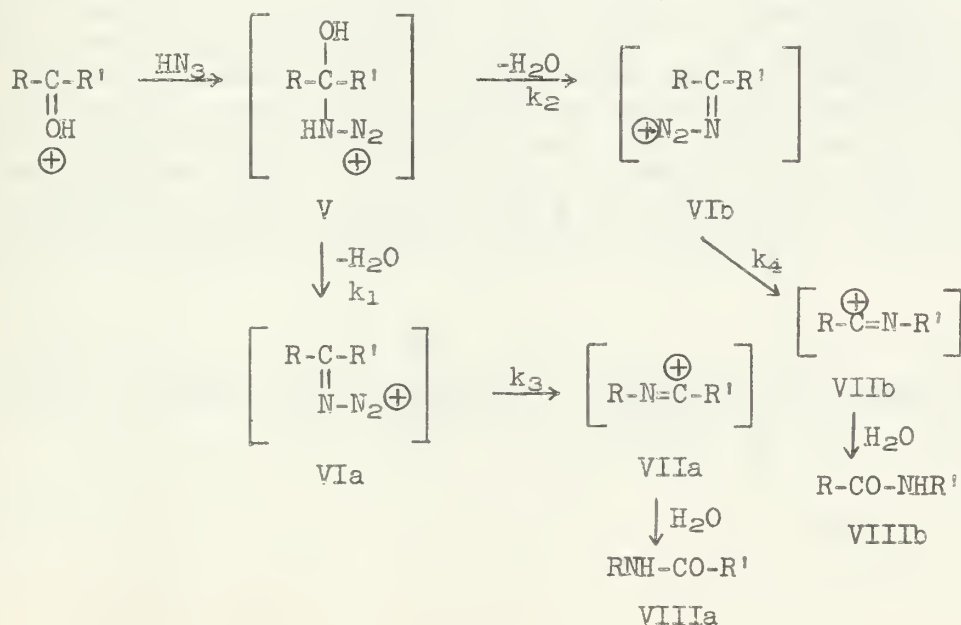
Introduction - The reactions of various carbonyl-containing compounds with hydrazoic acid in the presence of sulfuric acid as catalyst has been termed the Schmidt reaction. As the overall scope of this reaction has been reviewed elsewhere (1, 2b), this abstract will be limited to a discussion of the mechanism and scope of the Schmidt reaction of ketones.

The reaction of symmetrical ketones with hydrazoic acid produces a single amide as the main reaction product; unsymmetrical ketones usually form a pair of isomers in unequal amounts. The extent to which side-products such as nitriles (I), 1,5-disubstituted tetrazoles (II), ureas (III), and 5-aminotetrazole derivatives (IV) are formed strongly depends on both the reaction conditions and the structure of the starting material:



The nitriles may react with another mole of hydrazoic acid to form tetrazoles (II). However, none of the other products which require more than one mole of hydrazoic acid for their formation can be obtained under Schmidt reaction conditions from those formed from less hydrazoic acid. This signifies that reactive intermediates are formed which, depending on conditions, can react further with hydrazoic acid or in other ways to give terminal products.

Mechanism of Amide Formation - The most generally accepted pathway for the formation of amides is that proposed by P.A.S. Smith (2,3). His mechanism involves attack of molecular hydrogen azide on the conjugate acid of the ketone to produce a protonated azidohydrin (V). Loss of water ensues giving an iminodiazonium ion. When the starting material is an unsymmetrical ketone, the iminodiazonium ion is capable of

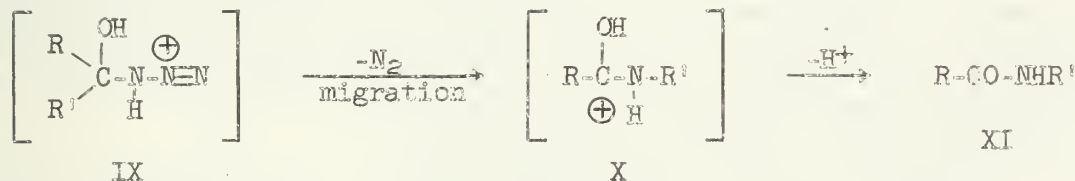


existing in two geometrically isomeric configurations (VIa and b). Loss of nitrogen with concomitant migration of the group anti to the diazonium nitrogens next occurs to give VIIa and VIIb. The assumption that the anti group migrates provides a way of explaining how steric factors may influence the ratio of the isomeric amides ultimately formed. The migration is analogous to that in the Beckmann rearrangement of oximes (4); indeed the ratio of isomeric amides formed in the Schmidt reaction often parallels the ratio in the corresponding Beckmann reactions (2). Ions VIIa and VIIb are then hydrated to form protonated amides. Addition of water in the reaction workup removes a proton from resulting protonated products to give the amides VIIIa and VIIIb.

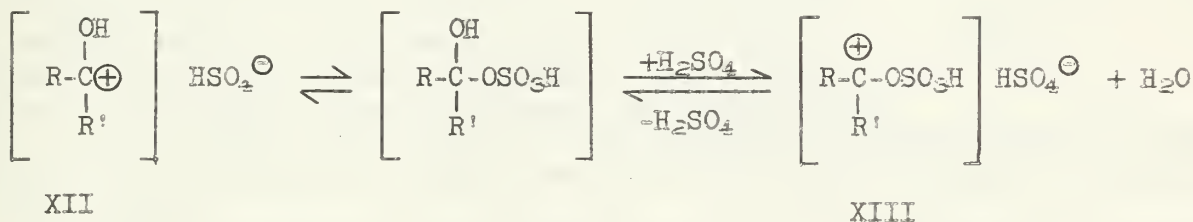
When the rates of rearrangement (k_3 and k_4) are faster than the dehydration rates (k_1 and k_2), the dehydration steps may be treated as being almost irreversible. The relative rates of dehydration (k_1 and k_2) are, then, considered approximately proportional to the thermodynamic stabilities of VIa and VIb. Thus the factors governing the relative stabilities of these two geometrically isomeric iminodiazonium ions would determine the ratio of products ultimately formed. This requires the assumption that the transition states for the dehydrations resemble the iminodiazonium ion products appreciably. The picture appears reasonable (2) since there is an extensive parallel between the ratios of isomeric amides produced in a Schmidt reaction and the equilibrium ratios of geometrically isomeric oximes of the same ketones (usually determined by examination of the amides formed from them by the Beckmann rearrangement). Moreover, both the oxime ratio and the amide ratio from the Schmidt reaction are largely in accord with the generalization that the more stable configuration is that in which the bulkier group is anti to the oxime hydroxyl (or diazonium nitrogens). Finally, these ratios generally are not influenced by electronic effects that determine the relative rates of decomposition (3a, 5).

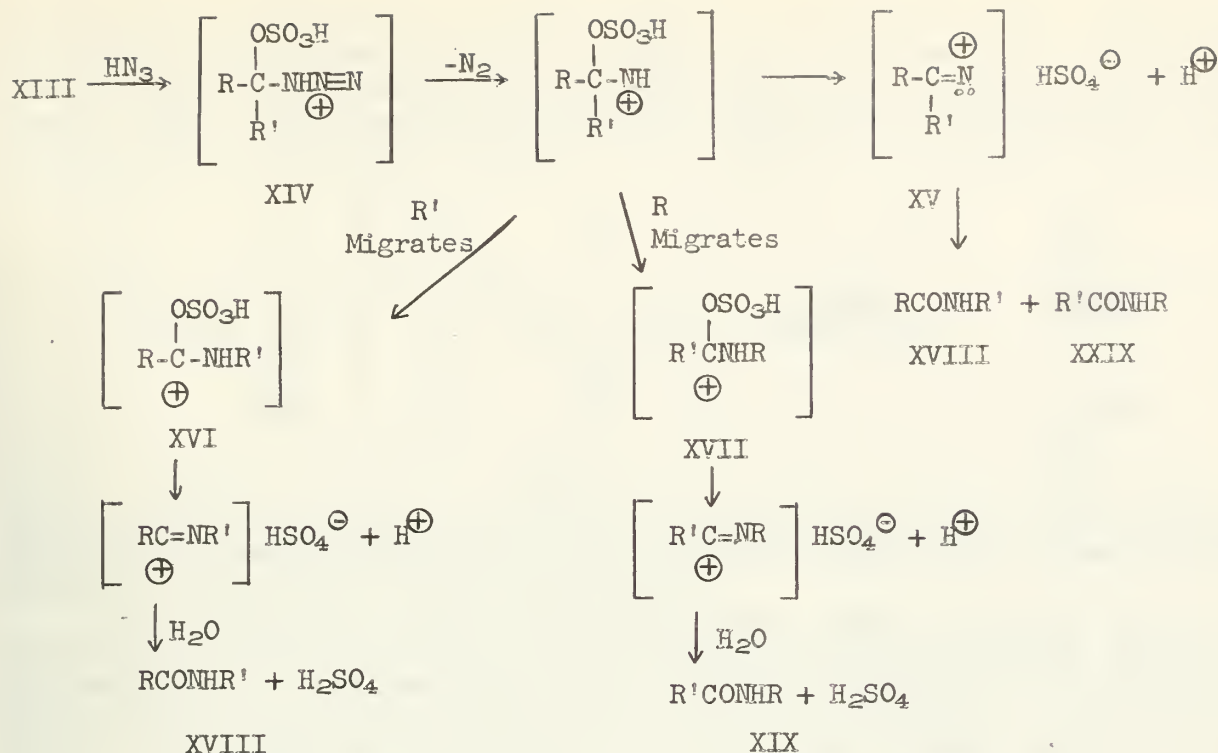
If, on the other hand, the dehydration steps were reversible and were faster than the rearrangement steps, equilibration between VIa and VIb would occur and the ratio of amide products ultimately obtained would be determined by the relative rates of rearrangement (k_3 and k_4).

Newman (6) suggested a mechanism which differs from Smith's only by the fact that dehydration never occurs in the reaction. According to Newman, the decomposition and migration may be represented by IX - XI.



On the basis of the half-lives of substituted ketones, Mirek (7) has proposed a mechanism in which the bisulfate ion plays a part. He suggested that the protonated ketone (XII) was attacked by the bisulfate anion and then dehydrated by a second molecule of sulfuric acid to give XIII which was attacked by the hydrazoic acid to give XIV. Three possible rearrangements may occur after loss of nitrogen: the bisulfate anion may be lost to give XV which rearranges and is hydrated to a mixture of amides (XVIII and XIX), or either R or R' can migrate to give XVI or XVII respectively which then loses the elements of sulfuric acid and is hydrated to the amide XVIII or XIX.

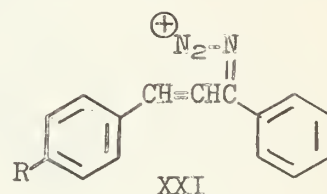
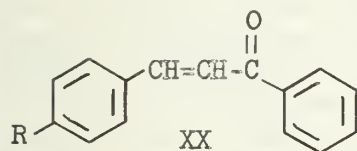




In the decomposition of XV, steric factors probably determine which group migrates (vide supra), but in the formation of XVI and XVII electronic factors were stated to determine the migrating group. Mirek stated that all rearrangements occur but only the most favorable prevails.

It should be noted here that the only basis for this mechanism is that the half-lives for the Schmidt reaction of various ketones (mostly benzalacetophenones) measured by Mirek at 14.8° (7a, 7b) were longer for those substituted with electron-donating groups (mostly halogens). Mirek states that this means that attack of the hydrazoic acid (evidently the rate determining step in his mechanism) is hindered by electron donation but that the decomposition of the resulting azide is facilitated. He found that the effect on the half-lives was the most pronounced with substituted benzalacetophenones (chalcones) (XX).

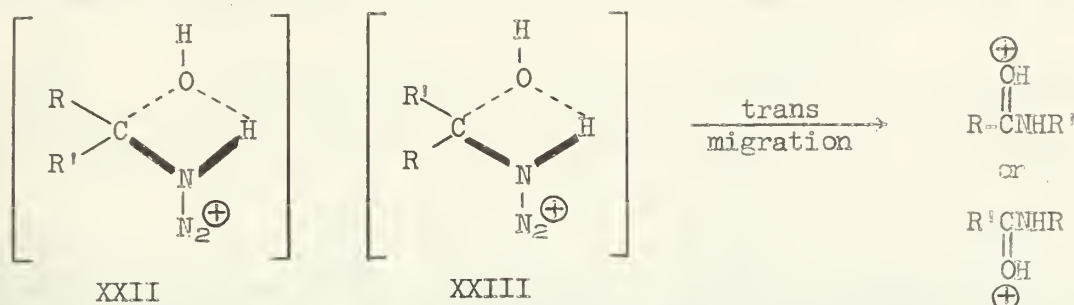
The only products he obtained were anilides of cinnamic acids in yields of 40-45% and an unspecified amount of tars. From this it is seen that at least 40% phenyl migration occurred. It is possible, therefore, to explain Mirek's results with Smith's mechanism, since the phenyl group is bulkier than CH in the vicinity of the carbonyl group. Thus the phenyl is probably anti to the diazonium nitrogens in the iminodiazonium ion (XXI) and phenyl migration would occur. If the tars obtained were due to products corresponding to styryl migration and not to starting material, an alternative explanation using the Smith mechanism would also be possible. Namely, the electron donors could cause the dehydration equilibrium to be faster than the rearrangement steps so that the relative amounts of the amide products would be determined by the relative rate of decomposition of the iminodiazonium ions. Here electron donation would accelerate that ion in which the styryl group is anti to the nitrogen leaving group. It is unfortunate that Mirek did not obtain the ratios of the two possible amides, as this would help distinguish between these two possibilities.



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Benzophenones, especially those substituted in the ortho position, are usually exceptions to the generalization that the more substituted group migrates. Arcus and coworkers (8) attempted to resolve this problem by proposing a different path for the Schmidt reaction. They stated that models of the protonated azide in the Smith

mechanism (V) show that the hydrogen bonded to the nitrogen closely approaches the oxygen atom when the molecule is in configurations XXII and XXIII. They suggested that hydrogen bonding between nitrogen and oxygen occurs, giving rise to a 4-membered chelate ring. This intermediate undergoes intramolecular rearrangement to give the conjugate acid of an amide directly. Arcus believed the nitrogen to be pyramidal and

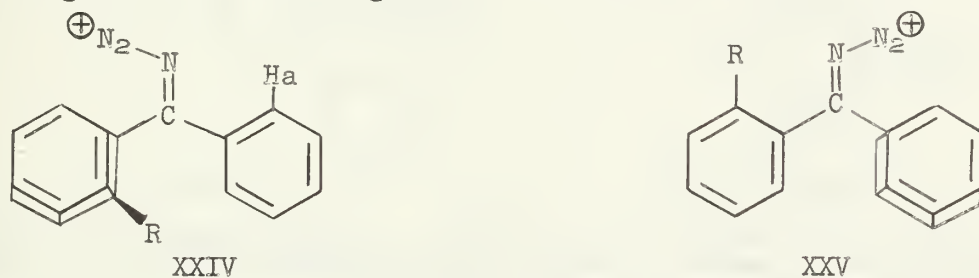


thus capable of existing in the above two forms. He also stated that the configuration of the diazonium nitrogens relative to the groups R and R' depends partly on electronic and partly on steric effects (8).

This mechanism has been severely criticized. Smith (2) stated that the same attractive and repulsive effects that determine configuration would operate between the same groups in the transition states leading to the chelate ring intermediate as in those leading to the iminodiazonium ions (VIa and b). Further, the energy of the hydrogen bond that completes the ring must be small at the strained angle of a four-membered ring (2a,7a) so that equilibration between geometrical isomers would not be slow (the usual condition in the Schmidt reaction). The cyclic intermediate provides no pathway for the formation of other products which are often formed in the Schmidt reaction.

Arcus' basis for postulating this intermediate was his assumption that sulfuric acid would not be likely to liberate water for the final hydration in the Smith mechanism and that this probably came from the work-up (8). To prove this point he worked up the Schmidt reactions of fluorenone and 2-nitrofluorenone using methanol as the diluent instead of water. If the water for the final hydration in the Smith mechanism came from the work-up, a methoxy derivative would have been found. Since none was obtained, Arcus suggested that water was not lost during the reaction sequence (i.e., XXII and XXIII were the intermediates). However, when the reaction was run in sulfuric acid-alcohol mixtures imidyl esters were isolated (2a). Smith also pointed to the fact that nitriles can be hydrated to amides by warming them in sulfuric acid. Further, if Arcus' reasoning were correct, it would be expected that sulfuric acid would dehydrate amides, in contrast to their known stability in that reagent (2a).

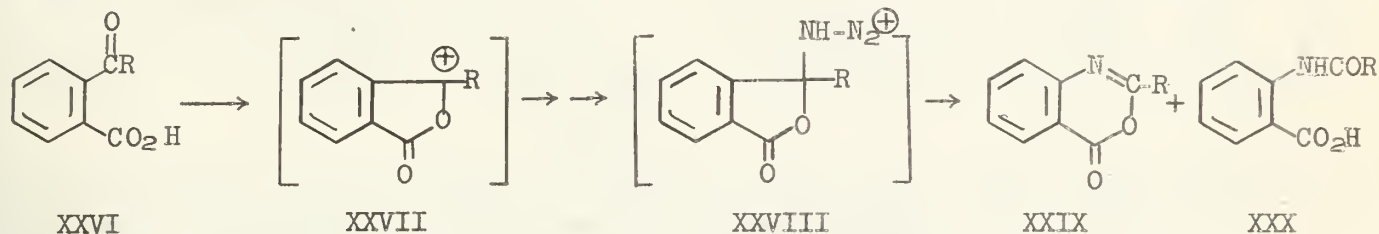
Smith (2) considered the anomalous ratios of amides from ortho-substituted benzophenones to be due to steric hindrance which prevents the substituted ring from being coplanar and in conjugation with the iminodiazonium group. This would cause the most stable configuration on steric grounds to be that of XXIV in which the perpendicular



axes of the two benzene rings are skew to each other and only the unsubstituted ring is in conjugation. Interference between the hydrogen in the outer, up-ended ortho position (Ha) and the diazo group on the nitrogen causes the more stable configuration to be anti to the unsubstituted group.

Now, if the electronic character of the substituent promotes conjugation, the most stable configuration would be that of XXV which is the geometrical isomer of XXIV. The amide ratio found would be the result of a combination of the simple bulk effect and promotion of conjugation (2).

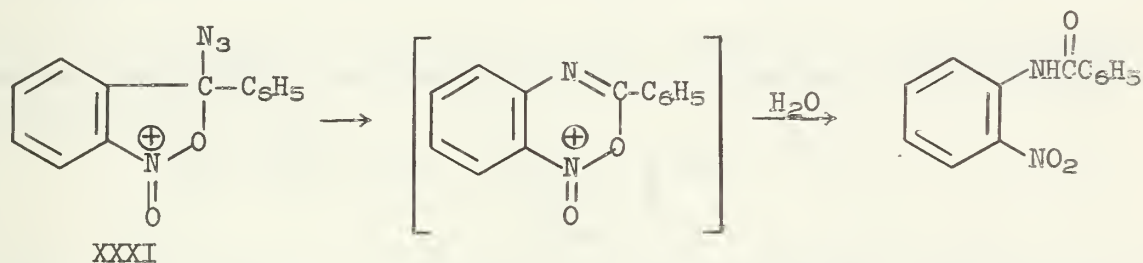
Three ortho-substituted benzophenones require further comment. The o-carboxy-, o-nitro, and o-phenyl benzophenones all show predominant migration of the substituted aryl group in the Schmidt reaction. Cyclization occurs for the o-carboxy compound to give a derivative of the lactol form (XXVIII, R = Φ) and the rearrangement is that of an azide rather than of a ketimine derivative (9a). Indeed both the oxazine XXIX (R = Φ) and the anthranilic acid XXX (R = Φ) have been isolated from this reaction (9c).



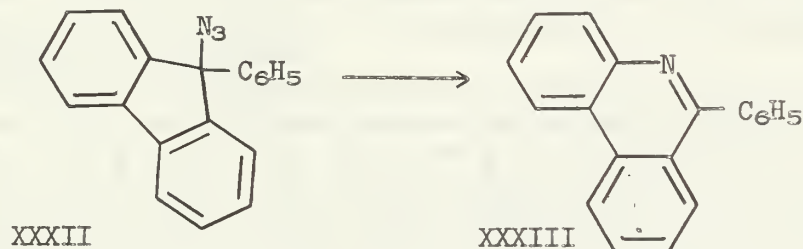
The postulated pathway (XXVI \rightarrow XXX) receives support from studies on benzylidene phthalide. This compound was protonated to give XXVII (R = $\text{CH}_2\Phi$) which, under the same reaction conditions as with o-phenylacetyl benzoic acid (XXVI, R = $\text{CH}_2\Phi$), reacted to give products XXIX and XXX (where R = $\text{CH}_2\Phi$) which were identical with those obtained from o-phenylacetylbenzoic acid itself (9b).

Bhatt (10) also studied migrations in substituted o-benzoylbenzoic acids. He considered that the greater bulk of the o-carboxyphenyl group was responsible for its preferential migration over phenyl. However, this explanation can be rejected by the finding of Arcus (9b) that o-carboxyphenyl also migrated preferentially over the presumably bulkier mesityl group.

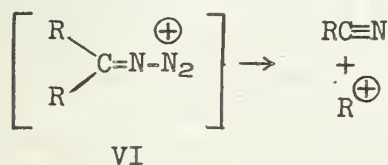
Since the nitro group and the carboxylate anion are isoelectronic, it is reasonable to propose analogous behavior for o-nitrobenzophenone (XXXI) (2). Szmant (11) has found such an interaction for o-nitrobenzoyl chloride. The Schmidt reaction of



o-phenylbenzophenone led to 9-phenylphenanthridine (XXXIII). 9-Phenyl-9-fluorenyl azide (XXXII) was said (2a) to be an intermediate. This then rearranged to the observed phenanthridine, a known reaction of 9-methyl- and 9-benzyl-9-fluorenyl azides (2a).



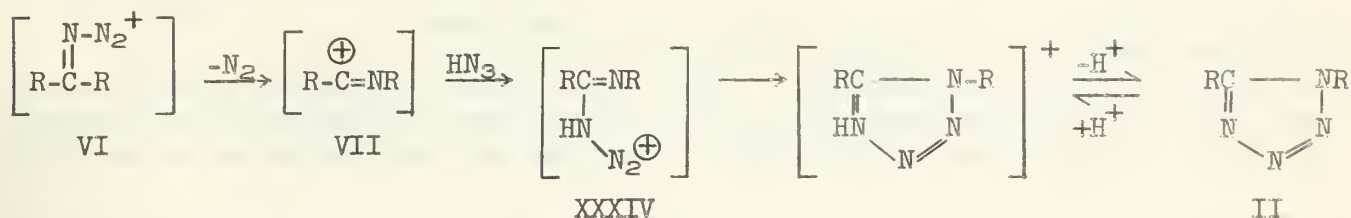
Formation of Other Products - Nitriles were formed as by-products when the imino-diazonium ion in Smith's mechanism (VI) fragments instead of rearranging in the process



of losing nitrogen. Zook and Paviak (13a) found with t-butyl alkyl and t-butyl phenyl ketones that alkyl or phenyl nitriles were formed. t-Butyl amine, formed from reaction of the t-butyl carbonium ion with hydrazoic acid, was also present in small amounts. If benzene was used as a solvent, mono- and di-t-butylbenzene were formed as well. Conley and Nowak (13b) studied the reactions of ketones which had α -spiro atoms and found that they gave ring opened unsaturated nitriles as well as unsaturated

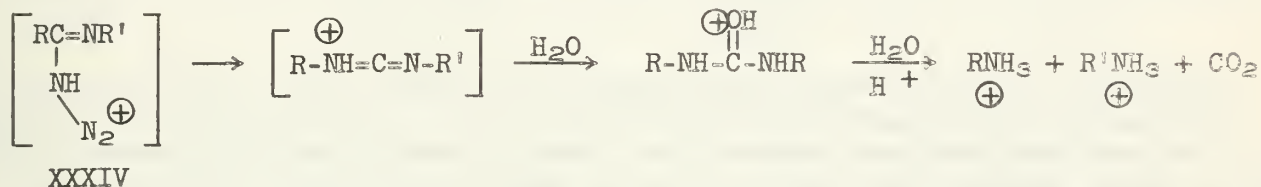
ketones from the acid catalyzed ring closure and hydration of the nitriles.

Tetrazoles are the usual side-products of the Schmidt reaction. If an excess of hydrogen azide is present, it may attack the carbonium ion (VII) formed after the rearrangement of VI in the Smith pathway. The resulting imidyl azide (XXXIV) can

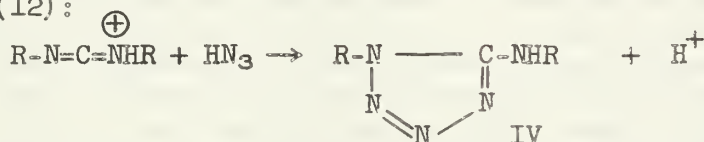


cyclize and lose a proton to give the tetrazole (II) (3c). Imidyl azides, prepared in other ways (2b, 12), will also cyclize to give tetrazoles.

Ureas are also formed as by-products. Attempts to make the tetrazole of 1-benzoylphenanthrene by preparing the imidyl azide using the reaction of the imidyl chloride with hydrazoic acid led only to the isolation of its carbodiimide which went to the urea with brief heating in acid. Further investigations (12a) led to the suggestion that ureas were formed by a protonated carbodiimide which arose by loss of nitrogen from and rearrangement of the imidyl azide (XXXIV). Carbodiimides are known to react with water to give ureas (12b). If the temperature at which XXXIV begins to rearrange faster than it cyclizes is low enough, the same products (ureas or amines)



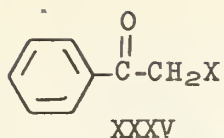
as from the decomposition of tetrazoles can be obtained in a Schmidt reaction. The carbodiimide may further react with hydrogen azide instead of water to give an amino tetrazole (IV) (12):



Scope of the Reaction - The reaction of o-substituted benzophenones has already been discussed. There it was determined that a balance between steric and electronic effects occurred and that the effect which governed the migration depended on the particular substituent involved. This can also be used to explain the reaction of o-amido benzophenones (14) which give the diamido derivatives if the substituent is o-benzoylamino, o-[o-nitrobenzoylamino] or o-propionylamino. The unsubstituted phenyl migrates in o-acetylaminobenzophenone.

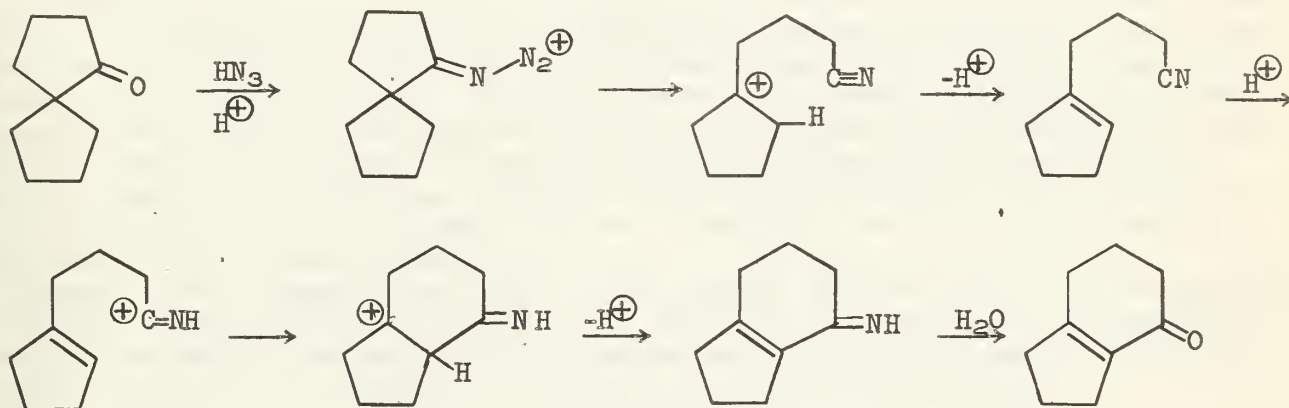
The Schmidt reaction with p-substituted benzophenones usually gives a 1:1 ratio of isomers (3b), but with p-methoxybenzophenone the anisyl group migrated by nearly 2:1 (3b, 14a). When the p¹-nitro- and p¹-chloro p-methoxybenzophenones were reacted, the ratio returned to 1:1 (15b). This was explained by applying to the iminodiazonium ion the observation that electron-withdrawing substituents on one phenyl group decrease the rate of rearrangement of the other in benzophenone oximes (2a). It is expected that such substituents would also decrease the rate of equilibration between the syn and anti forms of the iminodiazonium ion, an effect also said to be seen for the oximes (2a). Thus the p¹-nitro and p¹-chloro substituents would counterbalance the electronic effect of the methoxy group on migration ratios in p¹-substituted p-methoxybenzophenones.

Substituted acetophenones usually react under Schmidt conditions to give products corresponding to migration of the aryl group (16, 17, 18). As the alkyl group becomes more branched in the α -position in phenyl alkyl ketones, however, alkyl migration became more important (3b). However, with the limiting cases of pivalophenone (t-butyl phenyl ketone) and α -methyl- α -ethyl butyrophenone (19), products corresponding to



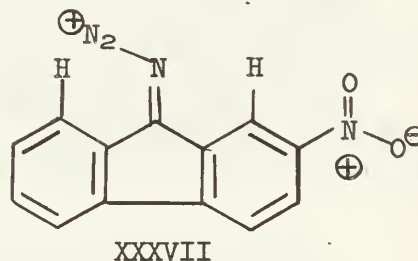
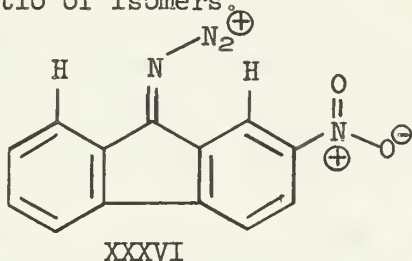
cleavage of the iminodiazonium ion were obtained. Acetophenones substituted on the methyl group (XXXV) with carbonyl containing compounds and others gave products corresponding to the migration of the phenyl group (5c).

As mentioned earlier, α -spiro ketones were found to give products corresponding to cleavage (13b, 20). A proposed mechanism is given below for spiro [4,4]-nonan-1-one (13b). The unsaturated nitrile formed in this mechanism has been isolated and found to undergo reaction in acid to give the same products as the ketone starting material. With cyclic ketones (21a-g), cyclic and

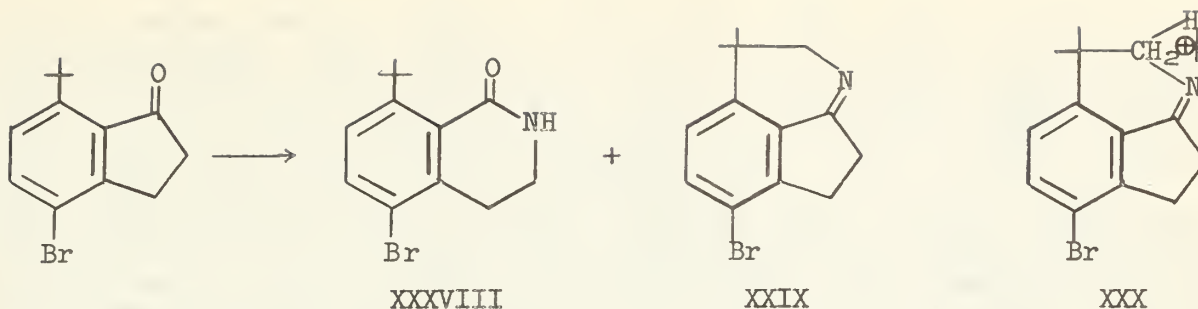


other diones (22a,b), acyl substituted benzene ring systems (5d, 22c), indenones (22d, e), and tropolones (22b), the usual products were those where the most substituted carbon atom had migrated although both isomers were sometimes obtained.

2-Substituted fluorenones present a system in which both benzene rings are held coplanar. This system is slightly strained as there is interference between an ortho-hydrogen and the diazonium nitrogens in the iminodiazonium ion in which a syn phenyl group is coplanar with the C=N double bond. A similar effect was mentioned earlier for benzophenones. Since the 2-nitro group is coplanar with the ring because of conjugation, there would be additional strain if the hydrogen tried to bend towards it in the 2-position. Thus the syn configuration (XXXVI) of 2-nitrofluorenone iminodiazonium ion would be less stable than the anti form, (XXXVII) and the major product is expected to be that corresponding to migration of the nitro-containing ring (2). This occurred to an extent of 19:1 (8). The 2-methoxy and 3-nitro-fluorenones gave about a 1:1 ratio of isomers.



Polyphosphoric acid (5b, 21c) has been recommended and found to be a good solvent and catalyst for ketones which fail to react or which give poor yields under the usual reaction conditions. In this medium, 7-t-butyl-1-indanone gave products corresponding to migration of the less substituted carbon (XXXVIII) and reaction with the t-butyl group (XXXIX) (23). A three-center process (XXX) for the formation of XXIX was postulated. It was found for p-benzophenones (15a) that changes in sulfuric acid concentration do not affect the ratio of products. However, the best reaction conditions vary for the particular type of ketone investigated (3c). Aliphatic ketones react best with HCl in concentrated sulfuric acid; aryl alkyl ketones with trichloroacetic acid-sulfuric acid and diaryl ketones with sulfuric acid alone.



No detailed study of the effect of temperature on the overall yields and product ratios in the Schmidt reaction has been undertaken. Qualitatively it has been noted for the reaction of α -chlorocyclohexanone that an increase in temperature improves the overall reaction yield (5a). In the Beckmann rearrangement of ortho-alkyl benzo-phenones, a large increase in temperature was found to favor the minor isomer formed (2a) but the magnitude depended on the particular substituent involved. Such an effect may also be present in the Schmidt reaction so that caution must be used in strict interpretations of the product ratios in reactions run at temperatures different from the 60° usually employed.

Summary - The mechanism and scope of the Schmidt reaction have been discussed in this abstract. The mechanism of Smith (2,3) was found to account for the results of the reaction of various ketonic species with hydrazoic acid quite well. A survey of the ketonic systems which undergo the Schmidt reaction was also given.

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STABLE ACYCLIC ALIPHATIC CARBONIUM IONS

Reported by D. Druliner

July 22, 1964

Introduction.--Studies of simple acyclic aliphatic carbonium ions have been reported in the chemical literature for a number of years. The existence of these carbonium ions has been inferred from conductivity and kinetic data, as well as from considerations of the steric course of certain reactions. Only rather recently have physical methods been employed for direct measurements on carbonium ions. The subject of this abstract will be the consideration of recent results in the detection and isolation of stable acyclic aliphatic carbonium ions. Reviews have appeared in which reactions between olefins, alcohols, and alkyl halides with strong acids are discussed (1,2,3).

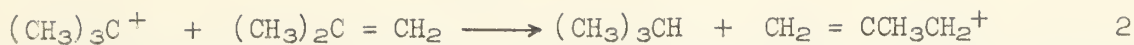
Carbonium Ions in Sulfuric Acid Solution.--Deno and Newman (4) reported that on the basis of cryoscopic measurements, dilute solutions of *t*-butyl alcohol ($6.4 \times 10^{-2} M$) in concentrated sulfuric acid gave rise to a van't Hoff *i* factor of 2 initially but that the *i* factor increased gradually with time to a value somewhat greater than 5. Development of a separate hydrocarbon layer with evolution of sulfur dioxide occurred when solutions were allowed to stand. In order to account for the change in *i* factor, it was proposed that an initial rapid protonation occurs, giving rise to an *i* factor of 2, followed by a slow formation of *t*-butyl cation.



The increasing *i* factor is believed to be due to the increase in species present in solution as a result of oxidation processes in addition to dissociations. In a more recent study, Gonzalez-Vidal, et al, (5) reported on investigations carried out with solutions of 1-octene, specified only as dilute, in concentrated sulfuric acid. They observed the formation of an ultraviolet absorption maximum at $300 m\mu$ ($\epsilon = 3000$ in concentrated sulfuric acid). The intensity of this absorption was found to be a function of H_0 , the Hammett acidity function. It was further observed that an oxidation takes place at room temperature yielding sulfur dioxide, isobutane, and isopentane. The production of sulfur dioxide had the same functional dependence on H_0 as did the spectral intensity. On the basis of these results they concluded that the characteristic yellow color in sulfuric acid-olefin systems is the result of oxidation processes and is not due to formation of carbonium ions. The observation that oxidation processes occur in strong acid solutions and in a manner dependent upon H_0 is an important one. However, these results do not rule out the possibility of the formation of detectable quantities of carbonium ions.

In an attempt to detect stable carbonium ions by ultraviolet spectroscopy, Rosenbaum and Symons (6,7), studied sulfuric acid solutions of numerous aliphatic alcohols, olefins, alkyl halides, and allylic compounds. Unless otherwise stated in this abstract, all solutions employed by Rosenbaum and Symons for spectral measurements were prepared by dissolving dilute solutions of the reactant in acetic acid followed by rapid mixing of a one hundred-fold excess of cold 98% sulfuric acid (8). The resulting solutions were generally less than $10^{-3} M$ in olefin, alcohol, or halide. The spectra of solutions more concentrated than about $10^{-3} M$ showed a second ultraviolet band in the $350 m\mu$ region. The separation of a hydrocarbon layer for the more concentrated solutions was also noted on standing. The spectra reported for the solutions less than $10^{-3} M$ in reactant showed absorption maxima in one of three principle regions. Both *n*- and isopropanol gave a λ_{\max} at $296 m\mu$ with unspecified ϵ -values. The absorption of the solution of the isomeric butanols, *t*-butyl chloride, *t*-butyl bromide, isobutylene, and di-isobutylene ($(\text{CH}_3)_3\text{CCH}=\text{C}(\text{CH}_3)_2$) fell within the region λ_{\max} 290-293 $m\mu$. The ϵ -values for this series of compounds were all about 6×10^3 with the exception of di-isobutylene ($\epsilon = 10.4 \times 10^3$). The third region included values from 273 to 275 $m\mu$ for allyl chloride, allyl bromide, and allyl alcohol. The ϵ -values for these allylic compounds were all about 4.5×10^3 .

In order to account for these results, Rosenbaum and Symons first examined the possibility that the ultraviolet absorption may be that of the products of oxidation reactions and not due to carbonium ions. Three possible reactions were considered: a direct oxidation by solvent to form sulfur dioxide; oxidation by dissolved oxygen; and disproportionation of the type indicated by equation 2.



In order to test whether or not oxidation occurs in the reaction with tertiary alcohols, an attempt was made to see if sulfur dioxide was formed in such processes. The method used depended upon the observation that a solution of iodine and iodic acid in concentrated sulfuric acid reacted slowly with sulfur dioxide with liberation of iodine. It is believed that the reaction involves a tri-iodide positive ion (9,10). When the iodic acid test solution was mixed with solutions of methylcyclohexane and t-butyl alcohol, iodine was only precipitated from the solution containing methylcyclohexane. Rosenbaum and Symons concluded that sulfur dioxide is not a product of the reaction between sulfuric acid and tertiary alcohols and that no detectable oxidation by solvent occurs.

They also observed that degassed solutions of t-butyl alcohol in sulfuric acid gave a build up of the band at 293mμ which was identical to that found for non-degassed solutions. They, therefore, suggested that there was no detectable oxidation by dissolved oxygen. Had disproportionation occurred, then saturated products would be formed (equation 2). Since it was shown that sulfuric acid oxidizes methylcyclohexane, with concomitant formation of sulfur dioxide, it is very likely that the saturated product would also have been oxidized, giving rise to sulfur dioxide. The results reported for t-butyl alcohol rule this possibility out. Solutions of various possible oxidation products were studied spectrophotometrically to discover what product might have an absorption maximum at 293mμ. However, 2-methylpropane-1,2-diol, 2-methyl allyl alcohol, isobutyric acid, 2-hydroxy-isobutyric acid, acetone, and acetic acid all showed no absorption in the 300mμ region.

One further explanation for the absorption maxima in the 300mμ region considered by Rosenbaum and Symons was that of absorption by products of polymerization. In the case of di-isobutylene, there was an instantaneous build up of a band at 292mμ, followed by a further relatively slow growth until the apparent extinction coefficient had increased from about 5×10^3 to 10.4×10^3 . The explanation proposed is that depolymerization occurs to give two moles of t-butyl cation per mole of di-isobutylene. Unfortunately no results of a product analysis for confirmation of this point were reported.

In support of their contention that the absorption spectra obtained for various compounds are due to carbonium ions, Rosenbaum and Symons carried out rate studies on several isomeric butyl alcohols and butyl chlorides. Good first order plots of $\log (\text{Opt. Density} - \text{Opt. Density}_t)$ vs time were obtained for each of the isomeric butyl alcohols as well as for t-butyl chloride and sec-butyl chloride.

Rosenbaum and Symons (6) found, as reported previously by Gonzalez-Vidal, et al, (5) for 1-octene, that the intensities of the ultraviolet absorption bands are dependent upon acidity. For example, solutions of t-butyl alcohol in sulfuric acid were kept until their ultraviolet spectra were invariant. The parameter Q was then defined as $Q = \frac{[\text{carbonium ion}]}{[\text{olefin}]} = \frac{\epsilon_{\text{exp.}}}{\epsilon_{\text{max}} - \epsilon_{\text{exp.}}}$, where $\epsilon_{\text{exp.}}$ is the apparent extinction coefficient at 293 mμ at a given value of H_0 and ϵ_{max} is the extinction coefficient in 98% sulfuric acid solution. Plots of $\log Q$ as a function of $-H_0$ resulted in lines with unit slope. It was also noted that spectra of solutions of t-butyl alcohol in dilute aqueous sulfuric acid were transparent above 210mμ; addition of concentrated sulfuric acid resulted in an immediate and quantitative reappearance of the band at 293mμ. The dependence of the absorption intensity upon H_0 rather than on the J_0 function (11) was put forth as evidence that the equilibrium being observed is loss of a proton to give isobutene, rather than addition of water to give alcohol in the examples believed to give rise to t-butyl cation. This observation is supported by the rapid reformation of the 293mμ band upon increasing the acid concentration. Rosenbaum and Symons proposed that had alcohol or polymer been formed that this should have been a slow process. As further experimental evidence that the absorbing species is not something other than carbonium ions, these workers report that methanol and ethanol in 98% sulfuric acid are transparent above about 200mμ. Thus the 293mμ band cannot be ascribed to alkyl hydrogen sulfates, which are formed under these conditions. Since solutions of t-butyl alcohol have no absorption in the 300mμ region at zero time but do have an

extrapolated a factor of 2 at zero time (4), it is probable that t-BuOH_2^+ is formed very rapidly and is transparent in this region. Rosenbaum and Symons concluded that the most likely explanation for the absorption obtained in the $300\text{m}\mu$ region is that carbonium ions are present and absorb in this region.

In order to explain why tertiary carbonium ions absorb in the $300\text{m}\mu$ region, Rosenbaum and Symons (12) considered an isoelectronic series. They suggested that if the transition in a t-butyl cation is one which involves charge transfer from methyl toward the central carbon atom, then the isoelectronic trimethyl borane should have a similar spectrum but with a maximum at somewhat shorter wavelengths. They reported a λ_{max} for trimethyl borane in hexane at $260\text{m}\mu$ ($\epsilon=6000$). They also concluded that since trimethyl borane is planar, trimethylcarbonium ion (t-butyl cation) should also be planar. Another interesting comparison made was that the difference between the λ_{max} values for carbonate and nitrate ions ($14,000\text{ cm}^{-1}$) is close to the difference found for trimethyl borane and trimethylcarbonium ion ($15,800\text{ cm}^{-1}$). These observations, however, do not take into consideration the differences in polarities of the solvents and differences in the electronegativity and formal charge of the central atoms.

Solutions of simple aliphatic carbonium ions in concentrated sulfuric acid have been reinvestigated by Deno and his co-workers (13), who used n.m.r. as well as ultraviolet and kinetic data. They found that dilute solutions (10^{-4} to 10^{-6}M) of t-butyl alcohol in 96% sulfuric acid produce the same λ_{max} and extinction coefficients as the more concentrated solutions though at much slower rates. The results of kinetic experiments (14) showed that the absorption at about $300\text{m}\mu$ forms in the early stages (0-20%) by a process that is kinetically second order in t-butyl alcohol concentration. These kinetic results were interpreted by Deno and co-workers as ruling out the possibility of absorption by t-butyl cation. It was also found that t-butyl alcohol, isobutylene, and the 2,2,4-trimethylpentenes in 98% sulfuric acid all produce the same reaction mixture. The mixture contained about 50% of a sulfuric acid-soluble fraction and about 50% of a sulfuric acid-insoluble fraction. The latter fraction showed an absence of $\text{C}=\text{C}$ absorption in the infrared spectrum and an absence of vinylic hydrogens in the n.m.r.; it was a mixture of saturated hydrocarbons which were separated by distillation into a dozen or more separate fractions. These on the basis of their boiling points were apparently composed of $\text{C}_5\text{-C}_{18}$ compounds. The sulfuric acid-soluble fraction was found to contain largely 1,2-dimethyl-3-alkylcyclopentenyl cations. An absorption with a λ_{max} at $302\text{m}\mu$ was proposed by Deno and co-workers to be characteristic of highly alkylated cyclopentenyl cations. The use of λ_{max} values to distinguish between a highly alkylated cyclopentenyl cation and a linear pentenyl cation appears questionable, however, since the λ_{max} values reported by Deno and co-workers (15) for 1,2,3,4,4,5-hexamethylcyclopentenyl cation and 2,4-dimethylpentenyl cation are 301 and $305\text{m}\mu$ respectively. The ultraviolet spectra of variously diluted samples of t-butyl alcohol in sulfuric acid solution generated the curve shown in Fig. 1. The half-formation of the absorbing species at 35%

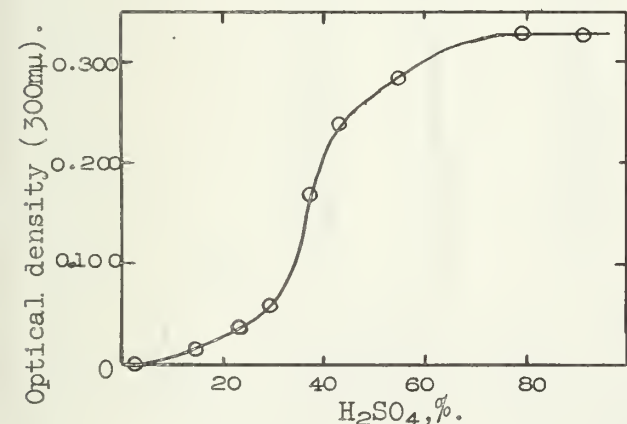


Fig. 1-Shift of equilibrium from cyclopentenyl cations (formed by addition of t-butyl alcohol to 96% H_2SO_4) to dienes on dilution of the H_2SO_4 solution. The experimental points have been corrected for the effects of dilution alone.

sulfuric acid is characteristic of 1,3-dimethylcyclopentenyl cations (15). The curve in Fig. 1 is distinct from that for linear alkenyl cations which exhibit half-formation values of 75% sulfuric acid. When the conventional drowning procedures developed by Whitmore and co-workers (16) were used for the neutralization of the concentrated sulfuric acid solutions of alcohols, only olefin polymers were isolated.

On the other hand, by rapidly dispersing the sulfuric acid solution through a capillary tube into vigorously stirred 10% aqueous sodium hydroxide, Deno and co-workers (13) have been able to isolate the sulfuric acid-soluble product. Fig. 2 is a comparison of the n.m.r. spectra of the dienes

(b.p. 55-60° at 20 mm.) isolated from treatment of 2,2,4-trimethylpentenes with 96% sulfuric acid with the dienes (b.p. 52-53° at 20 mm.) derived from the cationic species I (17). A direct comparison of the sulfuric acid-soluble fraction from the reaction with the linear 2,2,4-trimethylpentenes was also made, by means of n.m.r., with cation I in sulfuric acid. Deno and his co-workers regarded the

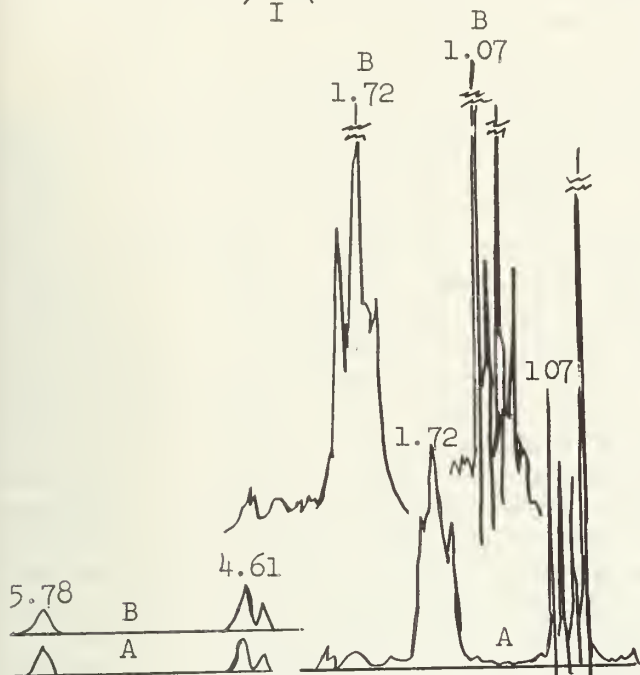
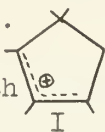


Fig. 2-(A) N.m.r. spectrum of the dienes derived from I (b.p. 52-53° at 20 mm.). (B) N.m.r. spectrum of the dienes (b.p. 55-60° at 20 mm.) formed from 2,2,4-trimethylpentenes. The solvent is CCl₄.

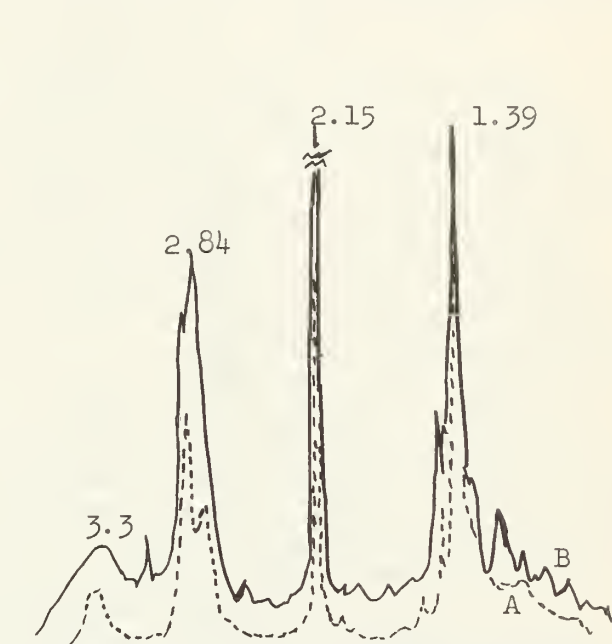


Fig. 3- (A) N.m.r. spectrum of the 1,2,3,4,4-pentamethylcyclopentenyl cation (I) in H₂SO₄. (B) N.m.r. spectrum of a H₂SO₄ solution of the cyclopentenyl cations derived from the dienes of b.p. 55-60° at 20 mm. which were obtained from the 2,2,4-trimethylpentenes.

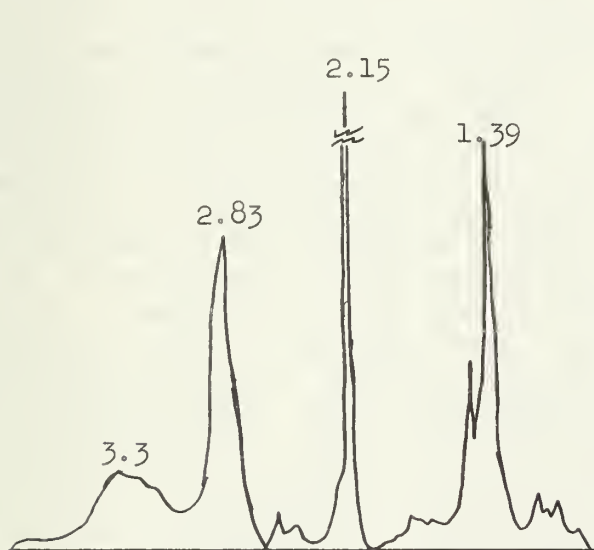


Fig. 4 - N.m.r. spectrum of a H₂SO₄ solution of the cyclopentenyl cations derived from the dienes of b.p. 55-75° at 20 mm. which were obtained from 2-butanol. An identical spectrum was obtained from a reaction starting with 1-butanol.

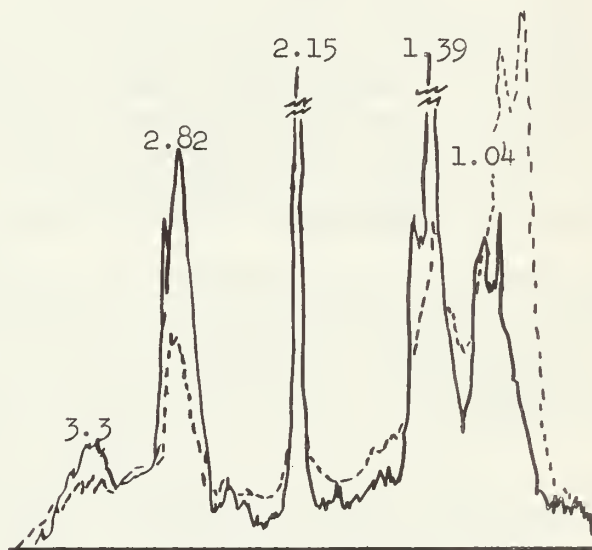
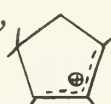



Fig. 5 - N.m.r. spectrum of a H₂SO₄ solution of the cyclopentenyl cations derived from the dienes of b.p. 100-110° (—) and of b.p. 150-165° (---) at 20 mm. which were obtained from the 2,2,4-trimethylpentenes.

very close resemblance of the various n.m.r. spectra depicted in Fig.'s 3 and 4 as supporting evidence that the species that absorbs at 302mμ is not a t-butyl cation. Reference to Fig. 4 shows a band centering at 3.38 (at lower field relative to tetramethylsilane), typical of H attached to C₄ or C₅ of cyclopentenyl cations (18). The band at 2.838 is characteristic of CH₃ or R-CH₂ groups at C₁ and C₃; and an unusually narrow band at 2.158 is characteristic of CH₃ on C₂. The relative areas of the bands at 2.838 and 2.158 was 2.0:1.0. From this ratio it was concluded that there are methyl groups at C₁ and C₂, and CH₃ or R-CH₂ at C₃ of the cyclopentenyl species.

The n.m.r. spectra of the sulfuric acid solutions of higher boiling dienes (b.p. 100-110; 150-165) were also reported and are shown in Fig. 5. The n.m.r. spectra in Fig.'s 4 and 5 are very similar except that as the molecular weight increases, the bands in the 0.5-1.58 region increase. This increase was explained in terms of an addition of hydrogens on carbon farther removed from the allylic system than either the α- or β-positions. The bands of the hydrogens on the α-(2.82, 2.158) and β-(3.38) carbon atoms stay much the same, showing that a central unit is maintained throughout the range of cyclopentenyl cations produced. In this connection, a gas chromatogram of the sample of dienes from authentic cation I, , exhibited a single unresolved band (despite the apparent presence of four different gem-dimethyl n.m.r. bands; Fig. 2). On the other hand, the dienes (b.p. 55-75°, 20 mm.) from 1-butyl alcohol, 2-butyl alcohol, and 2,2,4-trimethyl pentenes each exhibited a series of chromatographic peaks. One of the latter bands corresponded with the diene band derived from the authentic cation I band. This was taken as evidence that about 25% of the diene fraction from the sulfuric acid-soluble fraction was derived from I. The other chromatographic bands were believed to be due to dienes derived from higher and lower homologous cations such as II .

Because of the presence of absorbing species other than the monomeric cations, it is important to decide whether or not the n.m.r. spectra for linear cations truly represent valid measurements on the monomeric cations. It is perhaps not surprising that contradictory results concerning the state of the carbon species present in sulfuric acid solution (monomeric, dimeric, etc.) have been obtained; there is a large dependence on concentration of acid used as well as on the mode of mixing. Symons and Rosenbaum (6) reported a first order rate constant for the formation of the ultraviolet absorption maximum arising from treatment of t-butyl alcohol with sulfuric acid. On the other hand, Deno and co-workers (13), under very nearly identical conditions report a second order rate constant for development of the same band. In light of the results reported by Deno and co-workers, which indicate that the t-butyl cation could not be present in large enough concentration to be responsible for the build up the ultraviolet absorption, the results of Koch and Haaf (19,20) appear to be unexpected. These workers have obtained an 80% yield of adamantane-1-carboxylic acid from a reaction carried out by dissolving t-butyl alcohol in 96% sulfuric acid containing adamantane and formic acid to give a 4:1 ratio of t-butyl alcohol to adamantane. The proposal that the t-butyl cation abstracts an hydride ion from adamantane is substantiated by the fact that isobutane is given off.



The formic acid, which dehydrates in the presence of sulfuric acid to give carbon monoxide, is believed to react with the adamantane cation to form an acylium ion which subsequently leads to carboxylic acid. The fact that a 25% yield of trimethylacetic acid (CH₃)₃CCO₂H is also obtained in this reaction is good evidence of the intermediacy of the t-butyl cation. Many other branched carboxylic acids such as 2,2-dimethylbutyric acid Et(CH₃)₂CCO₂H have been prepared using this method.

In view of all the data thus far discussed concerning the t-butyl cation it seems likely that the existence of such species as stable monomeric entities is possible.

Deno and co-workers (18) have reported results from studies involving linear alk-enyl (allylic) carbonium ions which were investigated in partially monomeric form. Table I contains relevant n.m.r. data for two such species.

Fig. 6 shows the n.m.r. spectrum of the 2,4-dimethylpentenyl cation. Approximately 78% of the observed hydrogen appears in the form of unresolved extraneous background absorption. When the amount of diene added was reduced to a minimum and when it was added from a capillary into vigorously stirred 96% sulfuric acid at 0°, up to 50% of the total band area was due to the three bands of the 2,4-dimethylpentenyl cation

Table I

Compound	H on C ₃ , δ	CH ₃ on C ₂ or C ₄ , δ	CH ₃ on C ₃ , δ	areas	
				Exp.	Calc.
	7.70 *	2.97, 2.95 *		1:12.0	1:12.0
		2.95 **	2.12 **	3:14.5	3:12

* The bands and areas listed account for only 22% of the observed hydrogen

** The bands and areas listed account for only 40% of the observed hydrogen

(7.70, 2.95, and 2.97 δ). It was shown that if the diene is simply added dropwise with a slow stirring to 96% sulfuric acid at 25°, none of the hydrogen peaks is from 2,4-dimethylpentenyl cation.

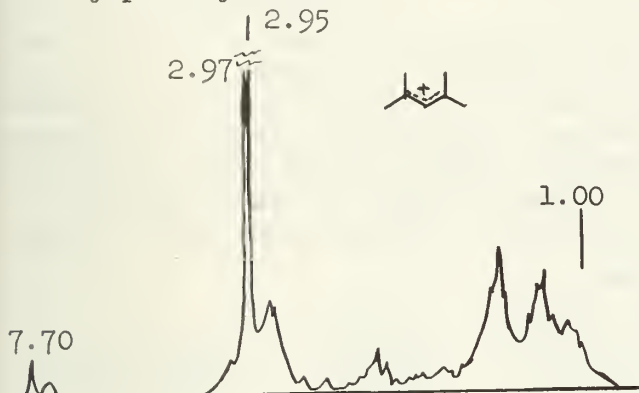


Fig. 6 -N.m.r. spectrum of 2,4-dimethylpentenyl cation showing the two sharp peaks due to the cation and the extraneous background caused by impurities.

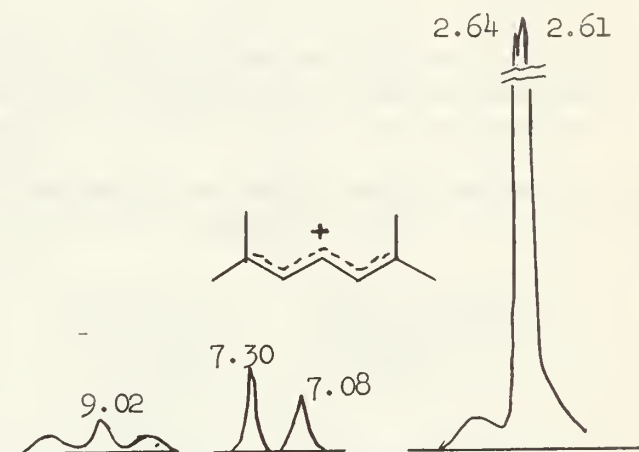
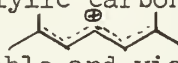
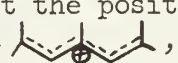
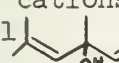

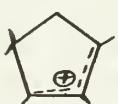


Fig. 7 -N.m.r. spectrum of 2,6-dimethyl-1,3,5-heptatriene in 96% H₂SO₄.

The results of studies with two diallylic carbonium ions were also reported by Deno and Pittman (21). The dienyl cation , generated from 2,6-dimethyl-1,3,5-heptatriene in 96% sulfuric acid, is stable and yields the n.m.r. spectrum shown in Fig. 7. The proton at C₄ (9.028) is farther downfield than the two hydrogens at C₃ and C₅ (7.198), in accord with an MO estimate that +0.33 charge resides of C₄ but zero charge on C₃ and C₅.

The separate bands for the two pairs of methyl groups indicate that the methyl groups do not equilibrate by rapid rotation about the C=C bond and that cis and trans isomers occur in dienyl cations as was found for alkenyl cations (18). The position of the methyl bands at 2.61 and 2.64 δ is at slightly higher field than the 2.95 and 2.97 δ bands found for the methyl groups in the 2,4-dimethylpentenyl cation, (Fig. 6). This in accord with the expectation that the positive charge is more diffuse in the dienyl cations. In contrast the cation , generated by addition of the dienylic alcohol  to 96% sulfuric acid, is very unstable as shown by its immediate conversion of  to .

Carbonium Ions in Antimony Pentafluoride

Solutions.—The preparation of stable alkyl carbonium hexafluoroantimonate salts has been reported recently by Olah and co-workers (22). When purified antimony pentafluoride was treated with vapor of t-butyl fluoride, a complex layer was formed. Successful preparations using all isomeric C₃, C₄ and C₅ alkyl fluorides were also achieved by adding the halide to a cooled (5–7°) solution of antimony pentafluoride or to a solution of sulfur dioxide (18°) containing excess of antimony pentafluoride. The complexes always contained excess antimony pentafluoride over that needed for the 1:1 complex; if this excess was not present no stable complex was formed. That indeterminable factors such as acid strength and solvating ability of the solvent employed, as well as the base strength of the alkyl halide, are important was demonstrated in a series of attempted preparations. For instance, attempts to obtain alkylcarbonium complexes by dissolving alkyl chlorides and bromides in the liquid Lewis acid halides stannic chloride, titanium tetrachloride, and antimony pentachloride were unsuccessful. It was found that the t-alkyl fluoride solutions could be diluted with other solvents other than antimony pentafluoride (sulfur dioxide, arsenic pentafluoride, and phosphorus penta-

fluoride) up to 10-15% excess antimony pentafluoride without appreciable change. However, when solutions of a secondary alkyl carbonium ion salt (dimethylcarbonium hexafluoroantimonate) were diluted, irreversible changes were observed in the spectra. These changes were attributed by Olah to the formation of cyclized alkylcyclopentenyl ions. In these cases, the less stable, less solvated carbonium ions are believed to undergo deprotonation to yield olefin which further reacts with excess carbonium ion. However, the evidence for the cyclopentenyl ions was not discussed.

In order to substantiate that the 1:1 adducts were truly carbonium hexafluoroantimonates and not merely donor acceptor complexes, Olah and co-workers made extensive n.m.r. studies. The F^{19} n.m.r. spectra of the carbonium hexafluoroantimonate complexes indicated the absence of covalent C-F bonds as shown by a single peak in accord with the hexafluoroantimonate ion. As Olah points out it is not possible to exclude the possibility of a rapidly exchanging, highly polarized $R-F \rightarrow SbF_5$ system. Also, the possibility of exchange involving solvent antimony pentafluoride can not be ruled out. Attempts were made to see if at lower temperatures, differences would be observable between the hexafluoroantimonate line and the one corresponding to an exchanging $R-F \rightarrow SbF_5$ system; but no changes were detected.

Several H^1 and H^2 n.m.r. spectra of the carbonium ion salts were obtained and discussed by Olah and co-workers. Table II summarizes the spectral data.

Table II

R	R-F, δ	J_{HF} , c.p.s.	$R^+ SbF_6^-$, δ	Peak area ratio
$CH_3-CH-CH_3$	-1.23	23.5	-5.06	5.95:1
	-4.64	48.0	-13.5	
$(CH_3)_3C$	-1.30	20.0	-4.35	
$(CH_3)_2C-CH_2CH_3$	-1.25	2.5	-2.27	2.96:5.97:2
	-1.55	20	-4.50	
	-1.85	24	-4.93	
$(CD_3)_3C$			-4.35	
$(CD_3)_2CD$			-13.48	
			-4.90	
$(CD_3)_2CCD_2CD_3$			-2.25	
			-4.47	
			-4.89	

The H^1 spectrum of the t-butyl cation consists of one sharp peak at δ 4.35 as compared to $(CH_3)_3C-F$ at δ 1.3. The t-amyl cation at 0° gave only partial resolution due to rearrangements. However, at -30° good resolution was obtained. It is interesting to find strong coupling of approximately 7 c.p.s. through the sp^2 hybridized positive carbon resulting in a well resolved triplet of the $(CH_3)_2CCH_2-$ methyl group protons at δ 4.50. It was observed by these workers that n-propyl and isopropyl fluorides gave the identical secondary carbonium ion complex with antimony pentafluoride. Similarly, all the isomeric butyl fluorides gave the same tertiary carbonium ion complex and only one tertiary carbonium ion was obtained from all seven of the isomeric pentyl fluorides. Thus isomerization to the thermodynamically most stable carbonium ion occurs. Also, no H^1-F^{19} coupling was observed for any of the carbonium ion complexes. Again, the possibility of fast fluorine exchange in the $R-F \rightarrow SbF_5$ system precludes taking this observation of no H^1-F^{19} coupling as conclusive proof of ionic dissociation. Perdeuterated carbonium ions were prepared for comparison, and reference to Table II reveals good agreement with the non-deuterated carbonium ions. One common feature of all the n.m.r. spectra obtained for the various carbonium ions was that of sizable deshielding of the protons as compared with the respective starting alkyl fluorides. It was pointed out by Olah that the deshielding effect of the central charged carbon is a very important factor. In this connection, Allred and Rochow (23) and Dailey and Shoolery (24) have shown that there is good correlation between chemical shifts and electronegativity in numerous saturated compounds. The possible extent to which the solvent antimony pentafluoride might affect the large H^1 chemical shifts was examined by a comparison of the trimethyl carbonium hexafluoroantimonate salt in the solvents antimony pentafluoride and sulfur dioxide. The solvent effect amounts to only about a 0.28 p.p.m. deshielding effect in antimony pentafluoride as compared with sulfur dioxide. However, in this

comparison it was mentioned that the sulfur dioxide solution contained an excess of antimony pentafluoride to stabilize the carbonium ion, so that the observed effect may be a minimal one.

Olah and co-workers also prepared trimethyl- and dimethylcarbonium hexafluoroantimonates labeled with C^{13} and obtained the C^{13} n.m.r. data given in Table III.

Table III

R	C^{13} chem. shift, p.p.m.	J_{C-H} , c.p.s. (CH)	J_{C-H} , c.p.s. (CH_3)
$(CH_3)_3C^{13}Cl$	0*		128
$(CH_3)_3C^{13} + SbF_6^-$	273		130
$(CH_3)_2C^{13}HCl$		151	127
$(CH_3)_2C^{13}H^+ SbF_6^-$		382	130

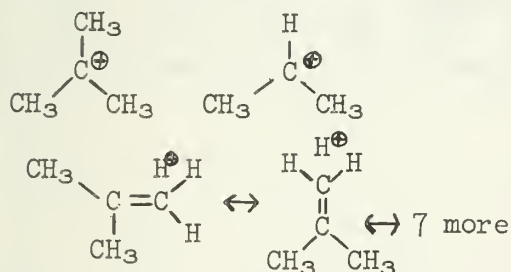
* C^{13} chemical shifts were calculated from $(CH_3)_3C^{13}Cl$ as reference.

The large shift of the C^{13} resonance line in the trimethyl carbonium ion complex, as compared with the position of the C^{13} line in the starting covalent sp^3 hybridized halide (273 p.p.m.), is difficult to interpret in any other way than as being very strong evidence that a carbonium ion has indeed formed. As might be expected the coupling data show no significant change in the C-H couplings of the methyl groups in the covalent alkyl halides or the carbonium ion complexes. However, the C^{13} -H coupling constant for the central carbon atom in isopropyl chloride changes from 151 c.p.s. in the covalent halide to 382 c.p.s. in the dimethyl carbonium ion. This large change indicates a marked increase in the s character of the C-H bond. The coupling constant is much larger than it is normally for an sp^2 carbon; perhaps the positive charge on the carbon is responsible for this anomaly. Again, Olah and co-workers feel that these data are difficult to account for otherwise than as being a consequence of change of hybridization and positive character of the central carbon atom in the ion.

The infrared spectra for the trimethyl-, dimethyl-, and dimethylethylcarbonium ions were also reported by Olah and co-workers.

In all cases, a broad absorption band was found near 1550 cm^{-1} which was dependent upon the purity of the antimony pentafluoride solvent, but the nature of the impurity was not established. It has been reported by Deno and co-workers (25) that for the case of cyclohexenyl cations, an intense absorption at 1533 cm^{-1} occurs. It is thus possible that secondary carbonium ions formed from the reaction with olefins due to deprotonation could add to the broad absorption found at 1550 cm^{-1} by Olah.

Two apparent discrepancies were found by Olah and co-workers regarding their infrared data. Using the trimethylcarbonium ion as an example, a strong C-H stretching fundamental occurred at 2830 cm^{-1} instead of in the usual range $2872\text{--}2962\text{ cm}^{-1}$ (26). Another strong band for the asymmetrical carbon skeleton stretching mode occurred at 1290 cm^{-1} instead of in the usual range $1200\text{--}1250\text{ cm}^{-1}$ (26). These features can be reasonably interpreted in terms of planar structures for the carbonium ions.



It is reasonable to assume contributions to these ions from nonbonded resonance structures such as those indicated for the *t*-butyl cation. The effect of these structures is to lower the C-H bond strength (lower normal frequency) and to raise the C-C bond strength (higher normal frequency).

As a further means of describing the carbonium hexafluoroantimonate salts, Olah and co-workers obtained ultraviolet λ_{\max} values for the various isomeric C_3 , C_4 , and C_5 alkyl fluoride-antimony pentafluoride salts. Due to experimental difficulties the extinction coefficient values could not be suitably obtained. All the absorption spectra consisted of a single weak absorption maximum around $290\text{ m}\mu$. The spectra obtained for solutions prepared with extreme caution in order to eliminate moisture and atmospheric oxygen showed no significant changes, indicating that oxidized allylic ions are not the primary absorbing species. These workers concluded that their ultraviolet data do not permit a definite assignment of the absorption maxima to simple carbonium ions because secondary deprotonation products could be present in low concentration.

Preliminary findings from studies of stable carbonium ion salts prepared by dissolving olefins; *t*-alkyl bromides, alcohols, and ethers; and isoparaaffins in hydrogen fluoride-antimony pentafluoride solutions have been reported by Brouwer and Mackor (27).

It is apparent that conflicting conclusions have been reached by different investigators regarding the nature of the carbonium ion species present in concentrated acid solutions. The disagreement among the various workers may be due to differences in their experimental conditions.

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STRUCTURE AND SYNTHESIS IN THE CARYOPHYLLENE FAMILY

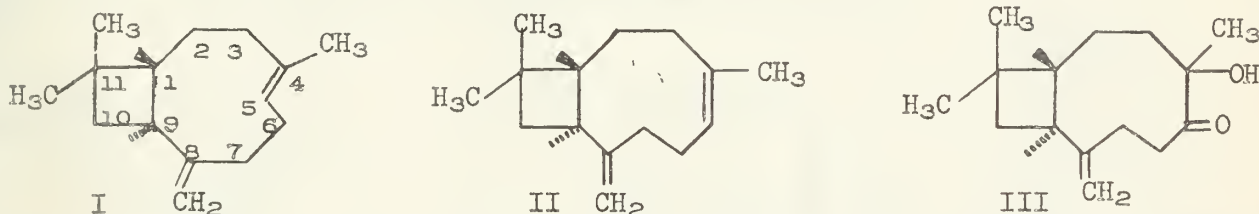
Reported by R.L. Keener

July 27, 1964

Introduction - After almost a century of intensive research, the structures of the sesquiterpenoid, caryophyllene (I), its geometric isomer, isocaryophyllene (II) and several of the tricyclic derivatives of I were finally established during the last decade. Recently the total syntheses of I and II (1) and of the tricyclic compounds, clovene (V) and α -caryophyllene alcohol (VIII), have been achieved. It is the purpose of this paper to define the structural relationships between these compounds and to describe their syntheses.

Structures of Caryophyllene and Isocaryophyllene - Caryophyllene (I) is one of the most interesting and remarkable members of the sesquiterpenoid family. It is readily obtained from oil of cloves, its major source, and has been the subject of numerous structural studies since around 1875 (2). However, most of the early studies of this compound were complicated by the fact that mixtures of unknown composition were employed in the experimental investigations and by the fact that mixtures of isomers were frequently encountered. Consequently, the structure of caryophyllene remained a hopeless puzzle until the early 1950's when, with the introduction of new physical methods of separation and analysis, rapid advances in the study of the caryophylenes began to occur.

It is now recognized that isocaryophyllene (II) differs from caryophyllene (I) only in the geometry around the endocyclic double bond (3,4) and that it is an artifact, derived from caryophyllene. The correct structure of caryophyllene was reported by Dawson, Ramage and Wilson (5) and its stereochemistry by Aeby, Barton and Lindsey (3). The early structural studies have been reviewed (6,7,8) and will not be presented here.

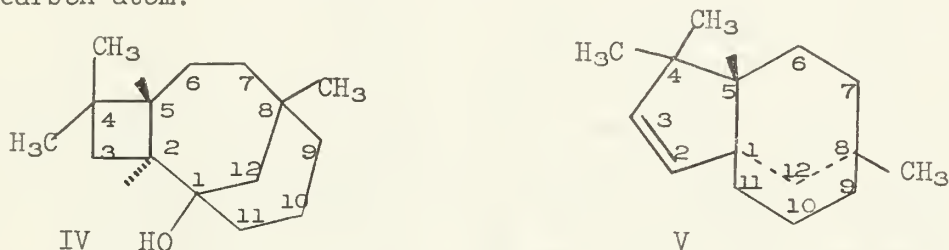


There are four structural units which distinguish the caryophylenes and from which results some unusual chemistry. These are the bicyclic skeleton composed of fused four- and nine-membered rings, the trans ring fusion between them, the exocyclic double bond and the endocyclic double bond. It has been established that caryophyllene has the trans and isocaryophyllene, the cis endocyclic double bond. Previously, the assignment of the geometry about the endocyclic double bond in these isomers was based on the observations that caryophyllene reacted with perphthalic acid and nitrous acid faster than did isocaryophyllene (3). Synthetic work (1) and other chemical studies (4, 15) have supported these assignments. Although the trans ring fusion in caryophyllene had been established by x-ray analysis in 1954 (10), the only evidence for a trans fusion in isocaryophyllene was the observation that caryophyllene, of unknown composition, was converted to isocaryophyllene via its nitrosite derivative (3). Corey confirmed the presence of the trans ring fusion in II by converting I to a secondary-tertiary glycol with OsO_4 -pyridine, oxidizing the glycol to the ketone, III, and converting this ketone to isocaryophyllene by Wolff-Kishner reduction and elimination.

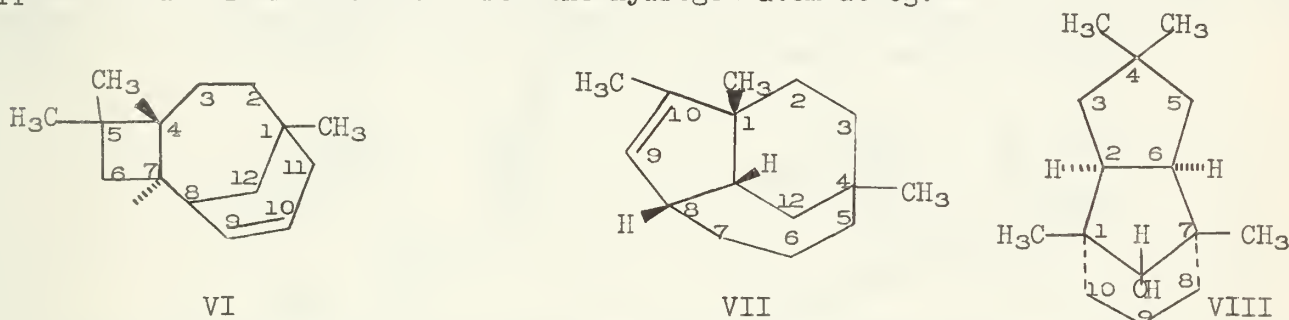
Skeletal Transformations - A look at the tricyclic derivatives resulting from the acid catalyzed rearrangement of caryophyllene provides some indication of the unique character of this molecule. The skeletal transformations of caryophyllene under a wide range of acidic conditions, the mildest of which appears to be with formic acid (9), yields two major tricyclic derivatives. One of these is caryolan-1-ol (or β -caryophyllene alcohol) (IV) whose structure has been determined by x-ray analysis on its chloro-derivative by Robertson and Todd (10). This investigation settled conclusively the question of the trans ring fusion in caryophyllene and also showed that the methylene bridge in caryolan-1-ol (IV) is on the same side of the molecule as the hydrogen atom at C_5 . The six-membered ring has the usual chair form, while the seven-membered

ring has the boat form. The four-membered ring is slightly distorted from the planar form.

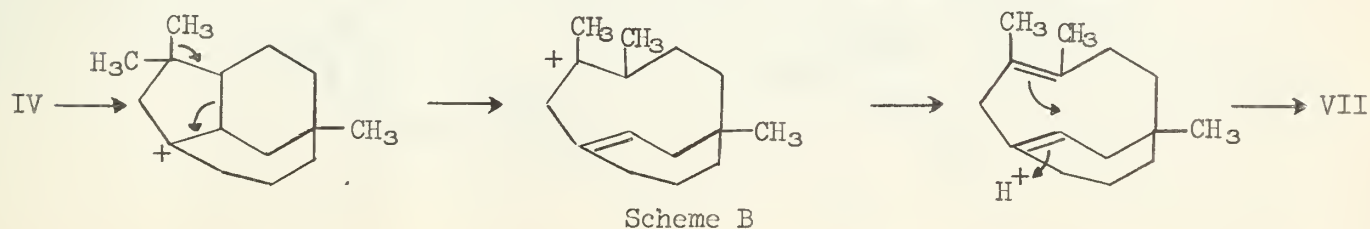
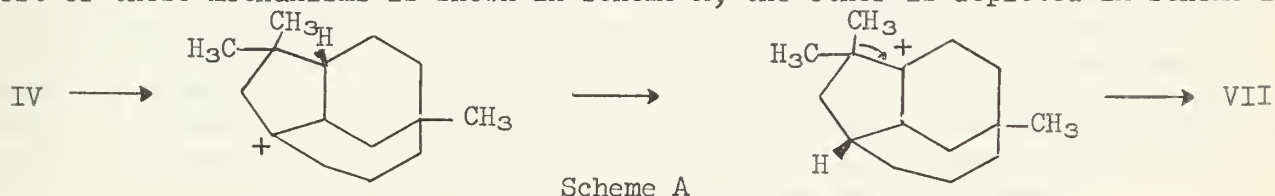
The formation of the chloro derivative by treatment of IV with phosphorous pentachloride (11) is of further interest in that its genesis from the alcohol (IV) represented one of the first examples of carbonium ion formation at a bridgehead carbon atom (12). Barton, Bruun and Lindsey (13) showed by chemical means that rearrangement does not occur during formation of the chloro compound from the alcohol (IV). Moreover, it has been shown that the chloro compound can be converted to the corresponding acetate by treatment with sodium acetate in boiling acetic acid (9). The chloro derivative, however, is unchanged by treatment with sodium ethoxide (9). These observations are consistent with an SN_1 mechanism for the substitution reactions at the bridgehead carbon atom.



The other major rearrangement product of caryophyllene is clovene (V) the structure of which was reported in a series of papers (13,14,15); its total synthesis has recently been described (16). It should be noted that the five-membered ring in clovene results from the migration of the C_1-C_9 bond in the caryophyllene molecule from the C_9 to the C_8 position and that the methylene bridge in clovene is on the opposite side of the molecule from the hydrogen atom at C_5 .

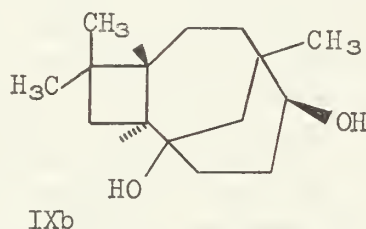
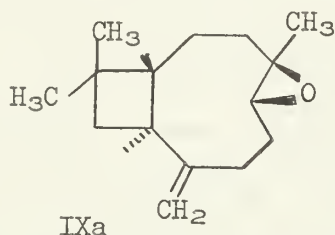


The fact that caryolan-1-ol is not converted to clovene using the same conditions under which clovene is obtained from I suggests that caryolan-1-ol, itself, is not an intermediate in the formation of clovene. This is further supported by the observation that under more vigorous dehydration conditions (17), clovene is converted to two new tricyclic derivatives, pseudoclovene (VI) and isoclovene (VII). The structure of the latter compound has recently been determined by x-ray analysis (18). Although there is insufficient data to establish the mechanism of formation of isoclovene from caryolan-1-ol, two possible pathways for the conversion have been proposed (18). The simplest of these mechanisms is shown in scheme A; the other is depicted in scheme B:



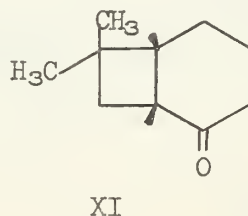
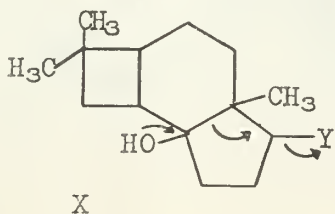
Until very recently it had been assumed that the acid catalyzed hydration of caryophyllene led to another tricyclic derivative, α -caryophyllene alcohol (VIII), whose structure has recently been determined by chemical means (19) and by x-ray (20). These authors (19, 20), however, showed that this compound (VIII) is derived from another sesquiterpenoid, humulene, which is obtained along with caryophyllene from oil of cloves. The total synthesis of VIII has recently been described (21).

The formation of the methylene bridge in clovene and caryolan-1-ol is readily explained by the proximity of the exocyclic methylene group and the trans endocyclic double bond in the nine-membered ring. It has been pointed out (15) that since the endocyclic double bond is trans in a nine-membered ring, its plane must be perpendicular to the plane of the four-membered ring and that the 4-methyl group in the caryophyllene molecule must point either in the same or opposite direction as the hydrogen atom at C₁. The authors (15) contend that since electrophilic attack on the endocyclic double bond would be expected to occur from the less hindered side of the molecule, the production of the two tricyclic derivatives, IV and V, is attributable to the existence of caryophyllene as a mixture of two conformers. While an inspection of Dreiding models indicate that caryophyllene may exist as a pair of difficulty interconvertible conformers, the chemical data casts some doubt on a simple conformational explanation. For example, the hydration of caryophyllene by concentrated H₂SO₄ in ether (17) is reported to give IV (ca. 40%) and a crude oil, containing clovene. However, treatment of caryophyllene with monoperphthalic acid in ether (19) produces in 77% yield (4) a single mono-oxide of caryophyllene (IXa) which corresponds to the conformer that would produce clovene on acid hydration of caryophyllene. A tricyclic diol (IXb) which corresponds to the conformer leading to caryolan-1-ol formation, is also obtained from the reaction mixture in about 10% yield. Treatment of isocaryophyllene (II) under the same conditions leads to the formation of two isomeric mono-oxides of isocaryophyllene (4). Additional experimental data will be required before a fully clear explanation of the formation of IV and V can be obtained.



Total Synthesis of d,l-Caryophyllene and d,l-Isocaryophyllene: The four major structural units discussed previously necessarily played major roles in the choice of the final synthetic approach toward the synthesis of the caryophyllenes. Corey and co-workers (1) decided to form the cyclobutane ring first since it would be relatively unreactive and more difficult to form at a later stage in the synthesis.

An attempt to fuse the nine-membered ring to an appropriately substituted cyclobutane derivative was made using the acyloin method. The attempt, however, showed little promise and since other methods of producing a nine-membered ring by direct fusion are less reliable than the acyloin method, an alternative experimental approach was considered more feasible. This alternative method involved the conversion of a cyclobutane derivative to a tricyclic compound from which a nine-membered ring could be formed by bond scission between two of the smaller rings. A bridged tricyclic compound was considered less suitable for this purpose than a fused tricyclic structure, and after consideration of several possibilities, Corey and co-workers selected X as the most suitable intermediate for the synthesis of the caryophyllenes.

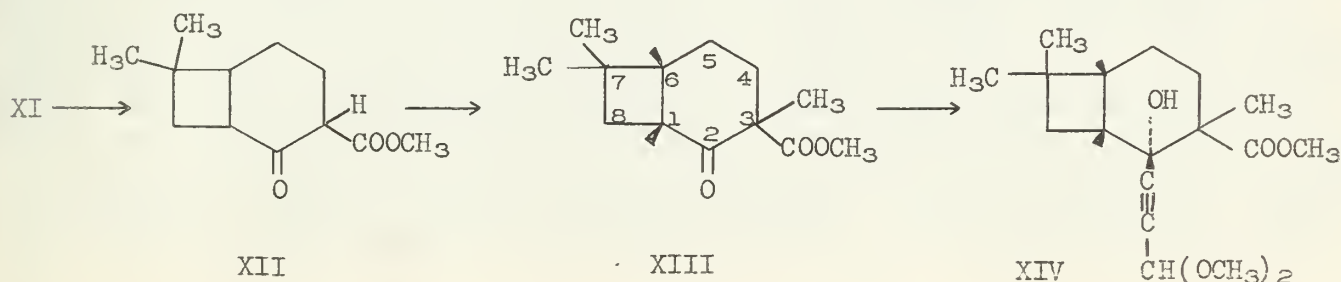


Such a model possesses several desirable features which allow control of the final product. Firstly, the geometry about the endocyclic double bond produced by internal elimination of the anionic leaving group, Y, can be controlled by the selective orientation of Y with respect to the adjacent angular methyl group (23, 24). Secondly, the production of a carbonyl function adjacent to the ring junction at C₉ by the internal elimination step provides a means of controlling the cis or trans nature of the ring fusion by epimerization. Finally, the resultant keto function can be converted to the methylene group by the Wittig reaction.

The first step in the synthetic scheme involved the photocatalyzed cycloaddition of 2-cyclohexenone to isobutylene at -40 to -70°C to yield the desired 7,7-dimethylbicyclo[4.2.0]octanone-2 (XI) in 35-45% overall yield. The structure of XI was verified by a variety of physical and analytical methods. The n.m.r. spectrum of the distilled product showed three sharp methyl resonance peaks at 8.85, 8.93 and 9.03 τ with intensities in the ratio of 5:4:1. When the sample was treated with base, the peak at 8.93 τ disappeared and there was a simultaneous increase in the intensity of the peak at 9.03 τ , equal to that of the peak at 8.85 τ which was unchanged by the base. Assignment of the peaks at 8.93 τ and 9.03 τ to the trans and cis isomers, respectively, of XI was supported by comparison of the n.m.r. spectra of the two isomers, the trans isomer being obtained by fractional distillation. The n.m.r. spectrum of XI also showed six sharp peaks in the region 6.9 - 7.4 τ corresponding to a single proton split into a pair of overlapping triplets by coupling with two equivalent protons and to a single additional proton. Since this resonance disappeared upon treatment of XI with deuterium oxide and potassium carbonate, this signal must be attributed to the bridgehead hydrogen atom adjacent to the carbonyl function.

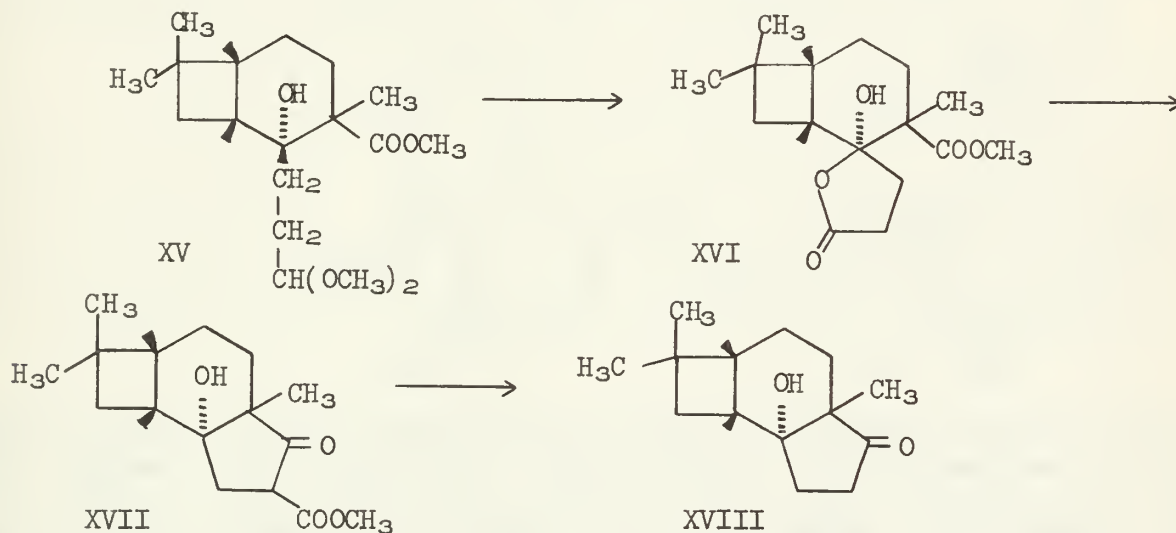
The results of this reaction were significant in two respects: Firstly, the 8,8-dimethylbicyclo[4.2.0]octanone-2 isomer was formed in only minor amounts, indicating an orientational specificity not previously encountered in similar reactions (25). Secondly, the n.m.r. spectra of the product revealed that the isomer with a trans ring fusion is formed in a ratio of 4:1 to the cis isomer. Related photocatalyzed reactions are well known (25) and are reported to yield the more stable cis adducts almost exclusively, as illustrated by the recently reported photocatalyzed dimerization of 2-cyclopentenone to two isomeric cis-anti-cis tricyclic ketones (26). However, deMayo has recently found (27) that irradiation of a solution of cyclohexene and methyl maleate gave the trans bicyclo[4.2.0]octane system in 19% yield, although cis adducts were still produced as the predominant species. Formation of another trans 1:1 adduct in a photocatalyzed cycloaddition reaction was described in a recent paper (21) on the synthesis of α -caryophyllene alcohol. This reaction involved the irradiation of a solution of 3-methyl-2-cyclohexenone and 4,4-dimethylcyclopentene in pentane. One trans and two cis 1:1 adducts were obtained from the reaction in relative yields of 14% and 86%, respectively.

The next five steps in the synthetic scheme were directed toward formation of the third carbocyclic unit of the intermediate, X. Reaction of XI with sodium hydride and methyl carbonate in dioxane produced the carbomethoxy ester, XII, with a cis ring fusion. This ester was then converted to a 3:1 mixture of stereoisomers of XIII by the addition of methyl iodide to a solution of XII and sodium hydride in dioxane. Since the stereoisomerism introduced in this step would be removed at a later stage in the synthesis, the mixture was used as such and no effort was made to ascertain the stereochemistry of the isomers. A solution of the keto ester, XIII, in tetrahydrofuran was then added to a freshly prepared solution of propargyl aldehyde dimethyl acetal to



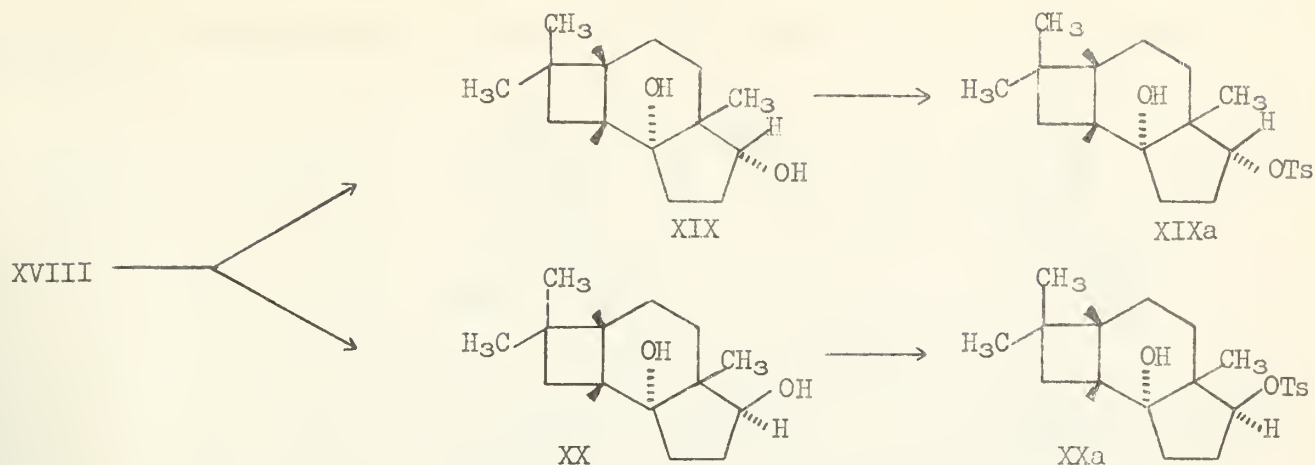
yield an acetylenic compound which had infrared and n.m.r. spectra consistent with structure XIV. The assigned stereochemistry at the C₂ position in XIV is based on the assumption that the acetylenic derivative will attack XIII from the same side of the six-membered ring that contains the bridgehead hydrogen atoms.

This adduct (XIV) was then converted to its tetrahydro derivative (XV) by hydrogenation using palladium on carbon in alkaline methanol. Acid catalyzed hydrolysis of XV yielded the corresponding cyclic hemiacetyl ester which, however, failed to undergo further cyclization to produce the third carbocyclic unit necessary for the formation of X. Consequently, XV was oxidized with chromium trioxide in acetic acid to the ester γ -lactone, XVI; the presence of both the lactone and ester carbonyl functions in this compound was confirmed by its infrared spectrum. Cyclization to the tricyclic β -keto ester, XVII, was accomplished by a Dieckmann type reaction using methylsulfinyl-carbanion in dimethyl sulfoxide as base (28). The product (XVII) was obtained in 57% yield and its infrared spectrum was consistent with the assigned structure. Hydrolysis of XVII with aqueous sodium hydroxide, followed by decarboxylation in pyridine at 110-115°, yielded the crystalline hydroxy ketone, XVIII. The n.m.r. spectrum of this compound showed three sharp methyl resonance peaks at 8.78, 8.90 and 9.02 τ , indicating it to be a pure isomer. A small amount of a higher melting ketone isomeric with XVIII was detected in the reaction mixture. Since the 4-6 ring fusion in XVIII is probably cis and since attack on XIII by the acetylenic derivative probably occurs cis to the bridgehead hydrogens in this compound, the ketone, XVIII, should have either a cis-anti-cis or cis-anti-trans structure. Although the cis or trans nature of the 5-6 ring fusion in XVIII was not determined, this point is of minor concern since the important consideration is the relative orientation of the secondary hydroxyl group (formed by reduction of XVIII) and the vicinal methyl group.

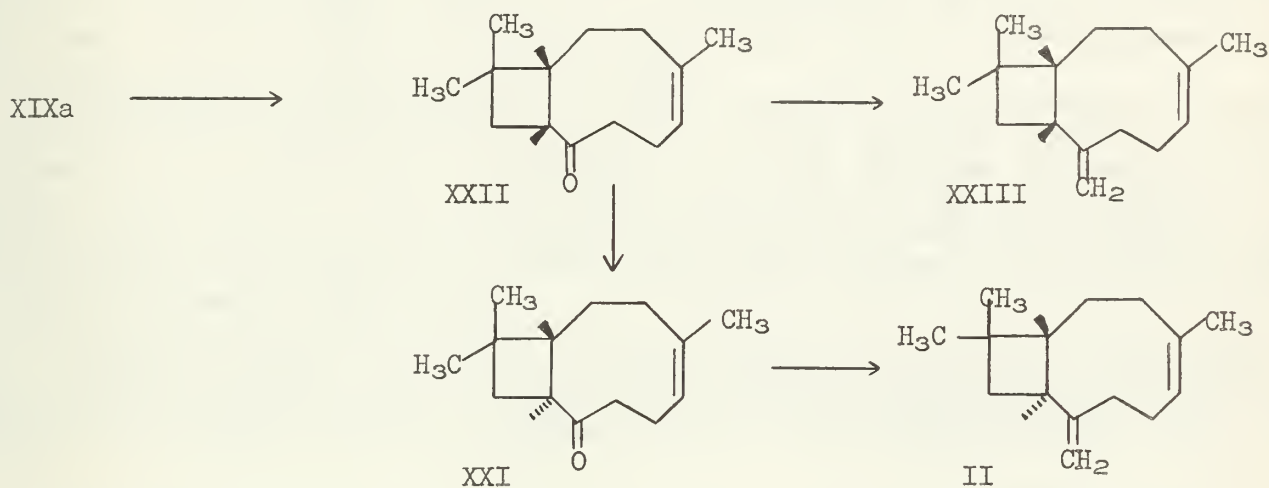


The next step in the synthetic scheme is the one which determines whether caryophyllene or isocaryophyllene will be the end product of the synthesis. This step involves the reduction of XVIII to either XIX or XX, in which the secondary hydroxyl group is either trans or cis, respectively, to the angular methyl group on the adjacent carbon atom. The secondary hydroxyl function can then be converted to the corresponding p-toluenesulfonate function and the resulting derivative subjected to a base catalyzed internal elimination reaction. If the internal elimination is concerted with respect to bond breaking and the stereoelectronically preferred coplanar mode of elimination occurs (23), the geometry about the resultant double bond will be determined by the relative orientation of the anionic leaving group and the vicinal methyl group. Thus the p-toluenesulfonate derivative (XIXa) of XIX should produce the cis olefin, and the analogous derivative of XX should produce the trans olefin.

Preparation of the diol, XIX, was accomplished by reduction of XVIII with sodium in moist ether or with a variety of metallic hydrides. The stereochemistry of this diol (XIX) was established by its subsequent conversion to isocaryophyllene. Hydro-



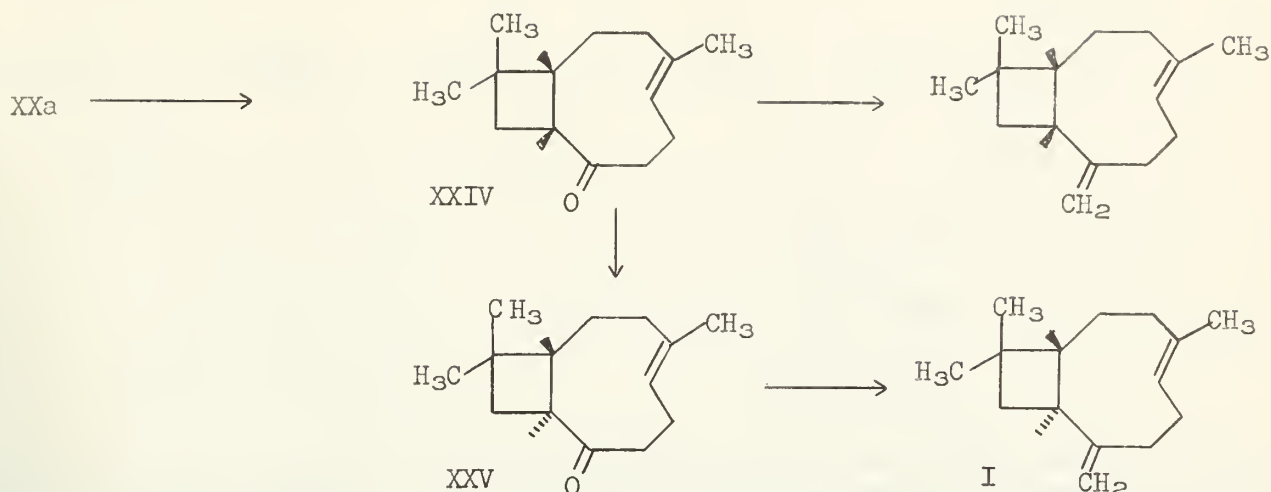
generation of XVIII using Raney nickel in ethanol gave a mixture of the diols, XIX and XX, which were separated by elution from a neutral alumina column. The infrared spectrum of XX differed in the C-O stretching region from that of the diol, XIX. Treatment of XIX and XX with p-toluenesulfonyl chloride in pyridine yielded the corresponding p-toluenesulfonate derivatives, XIXa and XXa, respectively. The former diol gave a non-crystalline p-toluenesulfonate, which differed in the infrared region normally associated with the tosylate function (29) from that of the crystalline XXa.



Treatment of XIXa with the methylsulfinylcarbanion in dimethyl sulfoxide (28) for 30 minutes, followed by the addition of t-butyl alcohol to allow isomerization to the trans ring junction, yielded the bicyclic compound, XXI. If the reaction was allowed to proceed for only 15 minutes and no t-butyl alcohol was added, another ketone (XXII) was obtained which was isomeric with XXI. The final step in the preparation of d,l-isocaryophyllene was the conversion of the ketone, XXI, to the corresponding methylene derivative by use of the Wittig reaction. Thus, the addition of XXI in dimethyl sulfoxide to a solution of methyl triphenylphosphonium bromide and methylsulfinylcarbanion in dimethyl sulfoxide (30) yielded a compound which was shown to be identical to natural isocaryophyllene by spectroscopic and chromatographic methods. Treatment of the isomeric ketone, XXII, with the same reagents and under the same conditions just described for XXI yielded a hydrocarbon which was isomeric with both caryophyllene and isocaryophyllene. Its infrared and n.m.r. spectra differed from those of either of these compounds, and it was assigned the structure XXIII.

Caryophyllene is obtained by a similar path from the diol, XX. Thus, treatment of XXa with a solution of sodium t-butoxide (prepared from sodium hydride and t-butyl alcohol) in dimethyl sulfoxide yielded the ketone, XXIV, after 4 hours and the ketone, XXV, after 15 hours. These two ketones were shown by v.p.c. and by infrared analysis to be different from one another and from the isomeric ketones, XXI and XXII. Since XXV was converted by the Wittig reaction to a hydrocarbon which was shown to be

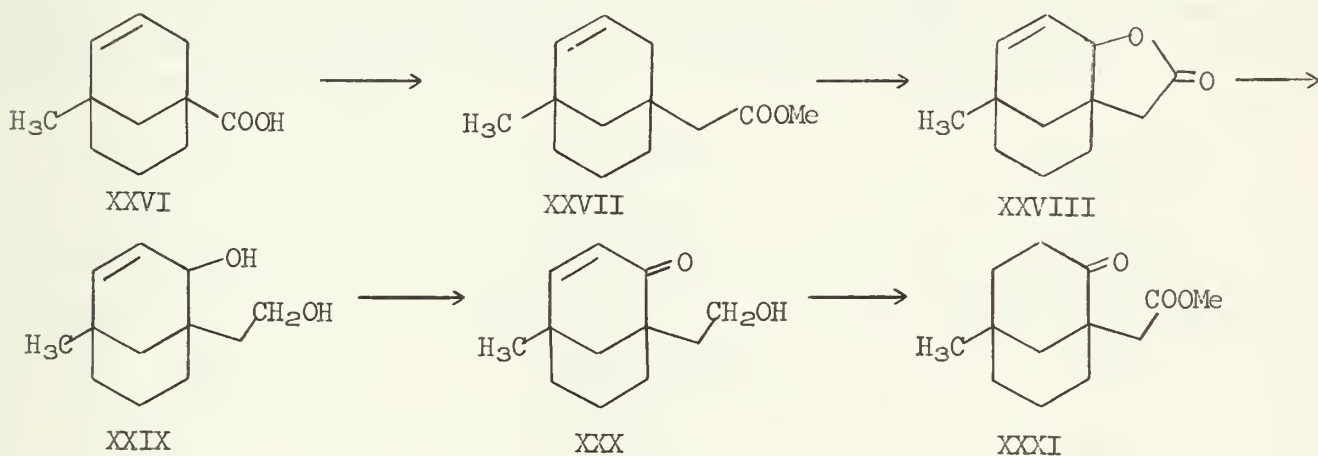
identical to caryophyllene (I), the ketone, XXIV, must have a cis ring fusion, as indicated.



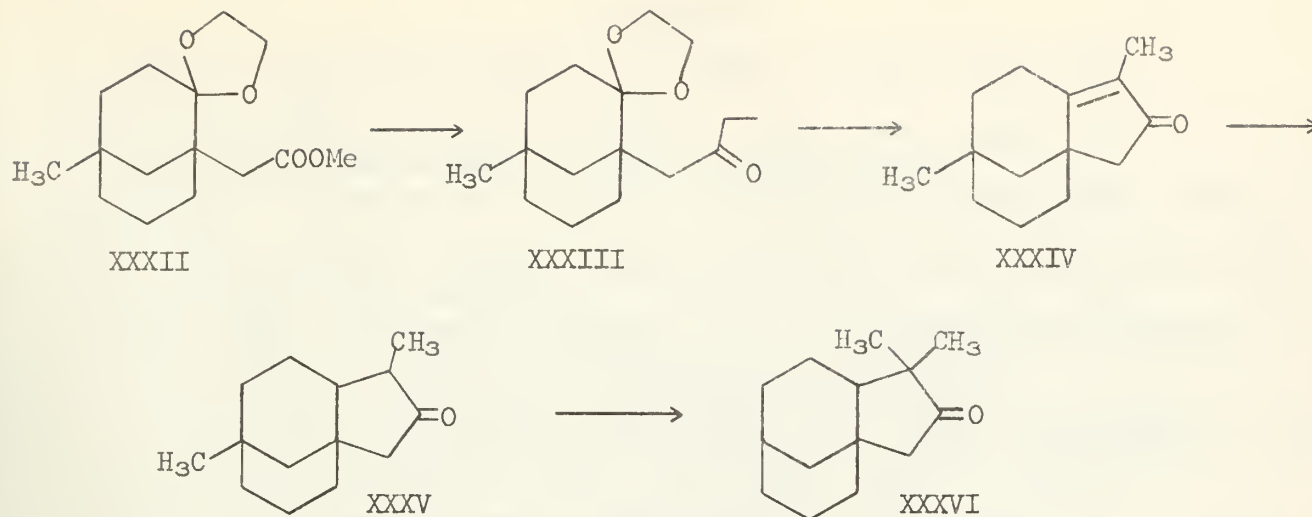
Corey and co-workers reported that the ketone, XXIV, was transformed to XXV much less readily than XXII was converted to XXI. They also noted that the same ketone (XXIV) failed to react with the Wittig reagent under conditions which led to the complete reaction of the other three ketones. These observations and the fact that an inspection of Dreiding models indicate the nine-membered ring in XXIV to be much more rigid than in XXII are cited by Corey as compelling evidence for the assignment of the trans endocyclic double bond to caryophyllene.

Total Synthesis of d,l-Clovene: The total synthesis of d,l-clovene has recently been reported in a communication and consequently, this synthesis will not be treated as extensively as those of the caryophyllenes. Partial syntheses of clovene have been reported earlier (31, 32, 33). The initial compound used in the total synthesis of clovene was the bicyclic acid, XXVI, whose preparation had been reported earlier (33). This acid (XXVI) was prepared in a three step synthesis starting with 2-ethoxycarbonyl-6-methylcyclohexanone and acrolein.

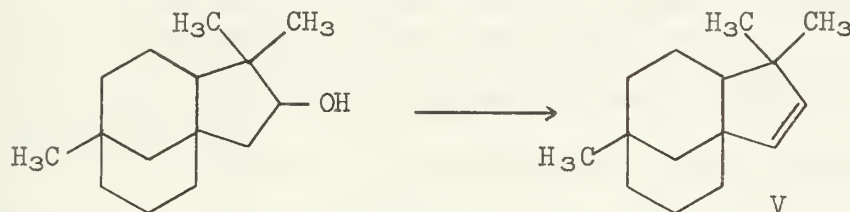
The bicyclic acid, XXVI, was converted by the Arndt-Eistert method (34) to the ester, XXVII, which upon reaction with selenium dioxide in acetic acid yielded the lactone, XXVIII. This lactone was reduced with lithium aluminum hydride to the diol, XXIX, which was then oxidized by manganese dioxide to the hydroxy-ketone, XXX.



The saturated keto-ester, XXXI, was prepared by oxidation of the ketone, XXX, with chromium trioxide, followed by catalytic hydrogenation and esterification. Formation of the ketal-ester, XXXII, was accomplished by reacting XXXI with ethylene glycol. This ketal-ester (XXXII) was then hydrolyzed to the ketal acid which was then converted to the ketal-ketone, XXXIII, by reaction with ethyl lithium. The derived diketone of XXXIII was cyclized by strong base to XXXIV which yielded the corresponding saturated alcohol by Birch reduction (35). This alcohol was then re-oxidized to the cyclopentanone derivative, XXXV.

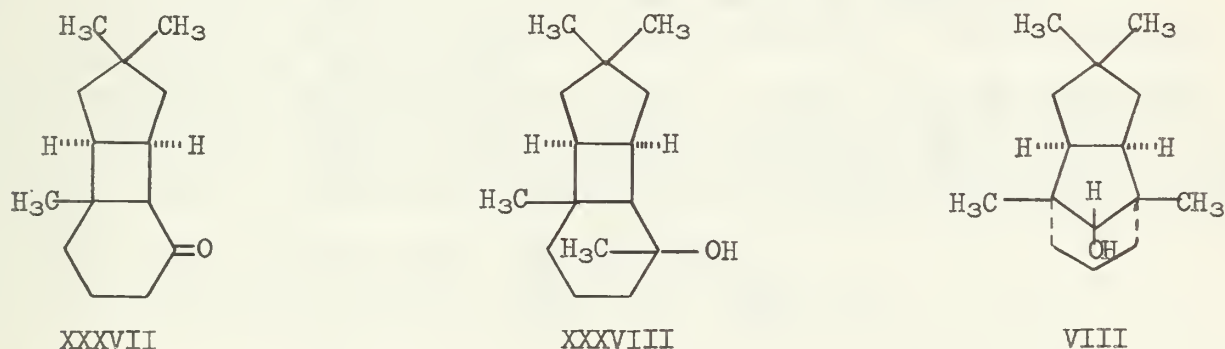


Methylation of XXXV yielded the gem-dimethyl homologue, XXXVI, which was converted to the corresponding alcohol by lithium aluminum hydride. Conversion of this alcohol to its carbonate derivative, followed by pyrolysis of the carbonate, yielded a compound, V, which after purification was shown to be identical to natural 1-clovene by a variety of physical and analytical methods.



Total Synthesis of α -Caryophyllene Alcohol: While α -caryophyllene alcohol (VIII) has been shown to be derived from humulene (20), the inclusion of its total synthesis in this paper is warranted by its long historical association with caryophyllene (I). The total synthesis of this compound in three steps has also been reported in a communication, and will therefore, be treated only briefly.

The first step of the synthesis involved the photocatalyzed reaction of 3-methyl-2-cyclohexenone and 4,4-dimethylcyclopentene in pentane. This reaction produced three isomeric 1:1 adducts of structure XXXVII in the ratio of 74:12:14. The predominant isomer was not isomerized by passage through a column of neutral alumina and was therefore taken to be the cis-anti-cis adduct. The assigned structure, XXXVII, was consistent with the analytical data.



The major isomer of XXXVII was converted to the crystalline tertiary alcohol, XXXVIII, by reaction with methyl lithium. The infrared spectrum of XXXVIII showed no carbonyl absorption and its n.m.r. spectrum revealed three singlet methyl peaks corresponding to 16 protons. Treatment of the alcohol, XXXVIII, with 40% aqueous sulfuric acid yielded synthetic α -caryophyllene alcohol (VIII) in approximately 50% yield. The synthetic compound was indistinguishable from natural α -caryophyllene alcohol by physical and analytical methods.

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CARBON 13 NUCLEAR MAGNETIC RESONANCE

By Leigh E. Walker

July 29, 1964

Introduction.--Early work on nuclear magnetic resonance (n.m.r.) was devoted to the proton and fluorine signals. The normal carbon 12 isotope does not interact with magnetic radiation and is of no use in n.m.r. spectroscopy. However, the carbon 13 isotope has a nuclear spin number of 1/2 and therefore can give n.m.r. spectra. In 1957, Lauterbur (1) and Holm (2), using the 1.1% of C^{13} in normal carbon, were able to obtain the C^{13} spectra of several organic compounds. The coupling constants J_{C-H} between carbon and the protons were also obtained. Several relationships between the properties of molecules and the observed chemical shifts and the coupling constants have been deduced from C^{13} and proton spectra.

The equipment required to obtain C^{13} spectra is essentially the same as that required for proton spectra. The carbon spectra are usually measured at a frequency of 15 Mc. The C^{13} proton coupling constants can be determined either from the proton or carbon spectra.

This abstract will consider only the C^{13} chemical shift (δ_c) and the C^{13} proton splitting. Some aspects of the earlier work in this field have been previously reviewed (3,4).

Carbon 13 Chemical Shift.--Many workers have reported values for carbon chemical shifts. The spectra are usually obtained using a C^{13} enriched external reference of either potassium carbonate or sodium acetate. Most workers then report their results relative to either carbon disulfide or benzene. The benzene signal occurs at 65 p.p.m. (higher field) on the carbon disulfide scale. All carbon chemical shifts reported in this abstract will refer to the carbon disulfide reference as zero.

Friedel and Retcofsky (5) have recently reported the chemical shifts for C^{13} in various positions in some hydrocarbons. Some of these shifts are given in Table I.

Table I

Chemical Shifts for C^{13} in Some Groups in p.p.m. From CS_2

Type Compound	Type Carbon	δ_c	Number of Cases	Type Compound	Type Carbon	δ_c	Number of Cases
Dienes	=CH ₂	76-83	5	Olefins	=CH ₂	78-88	9
	-HC=	55-7	3		-C ¹³ H=CH ₂	44-56	6
	>C=	48-50	2		>C ¹³ =CH ₂	41-9	3
Allenenes	=CH ₂	118-20	2		CH ₃ C=	70-7	6
	=CH-	102-10	3	Saturated Hydrocarbons	(CH ₃) ₂ C=	62-6	8
	=C=	-13 to -17	3				
Acetylenes	≡C-H	115-25				150-90	
	≡C-	108-19		Carbonyls		-25 to 40	

Certain trends are apparent from these data. The shift for the central carbon in an allene is very low while that for the acetylenic carbon falls at a high value. The carbon shift in the carbonyl is quite dependent on the groups to which it is attached. The substitution of a methyl or other group on a carbon chain lowers the shift, i.e. deshields, of the nearby carbons. Substitution of methyl groups on the 4 carbon in 2-pentene, increased the shift of the 2 carbon but decreased that for the 3 carbon. The shift of the C-1 ring carbon in toluene decreased as the α protons in the methyl group were replaced by methyl groups. The C^{13} shift is potentially a useful tool for the investigation of carbon skeletons. The C^{13} shift is a direct method for detecting acetylenic bonds in highly symmetrical molecules and tetrasubstituted carbon atoms. More extensive tables of spectra and correlations should increase the value of C^{13} n.m.r. in qualitative work.

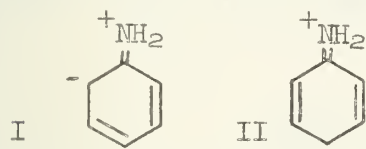
Lauterbur (6) observed that the shift for carbons in several nonalternate hydrocarbons eg. azulene, were larger than those for the alternate aromatic hydrocarbons. His conclusion that the shift depended principally on the π electron density ($\rho\pi$) in the ring has been supported by the work of Spiess and Schneider (7). The latter

workers have shown that the C^{13} chemical shift is directly related to the $\rho\pi$ at a given carbon. Using compounds of known $\rho\pi$, they plotted the $\rho\pi$ against δ_c . From this plot they obtained equation 1. Using equation 1, it was then possible to calculate the electron densities for the positions in azulene.

$$\delta_c(\text{p.p.m.}) = 160(\rho\pi - 1) \pm 65 \quad 1$$

The values obtained by this method were in good agreement with those obtained by other methods. Karpilus and Pople (9) have presented some theoretical equations to explain this correlation between δ_c and $\rho\pi$. It has also been observed (8) that the para carbon chemical shifts of several monosubstituted benzene compounds correlate with the Hammett para σ constants. The latter constants are normally considered to be related to the charge distribution at that position.

Recently Lauterbur (10) has studied a series of methyl substituted aromatic amines. The chemical shifts for the ring carbons in some anilines are given in Table II. It is apparent from the table that the negative charge density for aniline and N,N-dimethylaniline is high in the ortho and para position, consistent with the resonance forms (I and II) normally written for these compounds. As a methyl group is added in the



ortho position of aniline, the chemical shifts for the 4 and 6 carbons are relatively unchanged, indicating that the same type resonance forms are the important ones. However, when a methyl group is introduced ortho to the dimethylamino group, the shifts of the 2, 4, and 6 positions are decreased considerably, indicating that the resonance interaction is hindered by the ortho methyl group. This effect is more pronounced in the N,N-2,6-tetramethylaniline case.

Table II

Chemical Shifts (p.p.m.) for Ring Carbons
in Some Aromatic Amines

Compound	C-1	C-2	C-3	C-4	C-5	C-6
Benzene	65	65	65	65	65	65
Aniline	45.3	77.3	63.2	75	63	77.3
N,N-Dimethylaniline	42.2	79.9	64.0	77.0	64.0	79.9
o-Toluidine	47.2	70.2	61.8	74.8	65.2	78.3
N,N-Dimethyl-o-toluidine	39.8	61.4	61.7	69.7	66.6	73.9
2,6-Dimethylaniline	49.5	70.6	68.2	74.9	68.2	70.6
N,N-2,6-Tetramethylaniline	43.2	56.4	64.2	67.6	64.2	56.4

Dhami and Stothers (11) investigated the steric inhibition to resonance in a series of substituted acetophenones. As groups were introduced into the ortho position, the carbonyl carbon shift moved to lower field indicating that the resonance contribution of electron density from the ring had decreased. The authors suggested that there should be a relation between the C^{13} shift in an R substituted acetophenone and the angle θ between the carbonyl and the plane of the benzene ring and that this relation would be represented by equation 2. Acetophenone was used to give $\theta = 0^\circ$. The value of the shift for $\theta = 90^\circ$ was assigned on the basis of comparing the shift in going from acetaldehyde to acetophenone with that of adding phenyl groups to substituted

$$\cos^2 \theta = \left[\frac{\delta_c^R - \delta_c^{90^\circ}}{\delta_c^{0^\circ} - \delta_c^{90^\circ}} \right] = \frac{\delta_c^R + 23.2}{20} \quad 2$$

methanes. Using the observed shift δ_c^R the angle θ was calculated for several compounds. The values obtained were of the same order of magnitude as those derived from ultraviolet and dipole moment measurements. Since the latter values may have limited validity, a quantitative evaluation of the accuracy of the n.m.r. method can not be made at this time.

Several workers (6,8,10,12,13,14,15,16) have published data on the chemical shifts for other aromatic compounds.

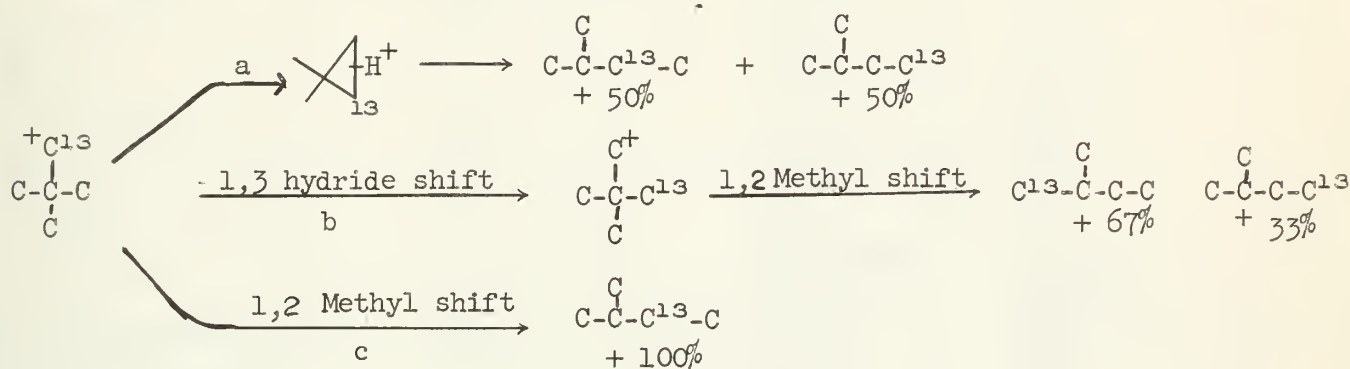
The chemical shift of C^{13} is normally not sensitive to solvents. However, it has been found that hydrogen bonding may affect the shift in a carbonyl carbon. Maciel and

and Ruben (17) studied the effect of solvent on the C^{13} signal in acetone. For a wide variety of solvents having either poor or nonexistent abilities to donate protons, there was a negligible solvent effect. The solvents having the greatest proton donating abilities, e.g. water and formic acid, gave the most negative chemical shift. The shift was not dependent on the dielectric constant of the solvent. Maciel and Savitsky (18) have reported negative shifts for some ortho-hydroxy aromatic carbonyl compounds. The shift for ortho-hydroxyacetophenone is 7 p.p.m. more negative than for acetophenone. This difference in shift is consistent with the intramolecular hydrogen bonding normally associated with this type compound and is not observed for other ortho groups.

C^{13} n.m.r. has been used to study the magnetic anisotropy effects of various substituents in methyl and ethyl compounds. This work has been reviewed (4) and will not be considered here.

Another potentially important use of carbon 13 lies in its use as a tracer in mechanistic studies. Karabatsos and co-workers (19,20) have employed C^{13} n.m.r. in their studies of the rearrangement of neo-pentyl carbonium ion to give the tert-amyl carbonium ion. Three possible paths for this rearrangement are given in Fig. 1.

Fig. 1



Starting with the neo-pentyl carbonium ion enriched with C^{13} in carbon one, the position and per cent label in each position in the products should be different for each of the three proposed paths. The reactions (deamination of neo-pentyl amine or solvolyses of neo-pentyl-p-toluenesulfonate or iodide) were run and the product, tert-amyl alcohol, was isolated and analyzed by n.m.r. The spectrum showed that all the C^{13} was in the 3 position, thus supporting path c and ruling out paths a and b. This method of carbon labeling has some distinct advantages over the normal C^{14} technique. Since the C^{13} isotope is not radioactive, there is no potential danger from handling it. Secondly and more important, the C^{13} analysis can be carried out quickly and conveniently on the product. For studies using C^{14} , it is necessary to convert the labeled carbon unambiguously into a fragment that can be counted.

Carbon 13 Proton Coupling.--Currently the splitting caused by the interaction of a C^{13} atom with a proton is receiving considerable attention. By using the natural concentration of C^{13} , a rather simple spectrum can be obtained. Since the C^{13} is present to the extent of only 1.1%, the chances that one molecule will have two adjacent carbon 13 atoms is quite low, thus eliminating the complications of further splitting. In Table III are listed the C^{13} proton coupling constants for several compounds together with the type of hybridization expected for the carbon atom studied. It will be noted from inspection of the table that the observed splitting depends upon the state of hybridization of the carbon. When the observed J 's were plotted against the % s character (R_{CH}) of the bond (21) a straight line resulted with a zero intercept.

Muller and Pritchard (22) and also Dreeskamp and Sackmann (30) have derived this relationship from basic n.m.r. theory. It is first assumed that only one electron pair contributes to the coupling. It is then assumed that the electron pair may be represented by a 2-center bonding molecular orbital of form 3 where $1s_H$, $2s_C$, and $2p_C$ are atomic orbitals and a and b are normalizing factors. If a contact mechanism, i.e.

$$\psi_{C-H} = a(1s_H) + b\left\{\sqrt{\rho_{CH}} \quad 2s_C + \sqrt{1-\rho_{CH}} \quad 2p_C\right\} \quad 3$$

the interaction between the s electrons and nuclear spins, is assumed to be predominantly responsible for the splitting, then the solution of the wave equation gives equation 4 where K is a constant, Z is the effective nuclear charge of the carbon in question and ΔE is the average excitation energy. The term $a^2 b^2$ has been shown to be relatively insensitive to changes in bond polarity and therefore may be taken as a constant. Likewise the excitation energy of the C-H bond should also be relatively constant. If the effective nuclear charge is also taken as a constant, then the coupling constant should be given by 5 from which 6 comes empirically.

$$J_{C-H} = \frac{KZ^3_{\text{eff}} a^2 b^2 \rho_{CH}}{\Delta E} \quad 4$$

$$J_{C-H} = K \rho_{CH} \quad 5$$

$$\rho_{C-H} = 0.2 J_{C-H} \quad 6$$

Table III

 J_{C-H} for Some Compounds

Compound	Hybridization C-H Bond	J (c.p.s.)	Reference
Cyclohexane	sp^3	124	23
Ethane	"	125	24
Acetone	"	126	25
Toluene	"	126	25
Formaldehyde	sp^2	172	26
Allene	"	168	27
Benzene	"	159	22
Biphenyl	"	162	6
Cyclohexene	"	156, 170	28, 21
Ethene	"	157	28, 24
Methylacetylene	sp	247	29
Acetylene	"	249	24
Phenylacetylene	"	251	22

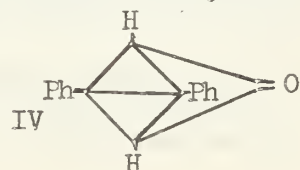
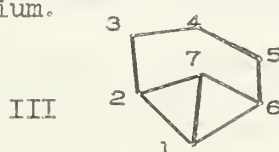
Once this relationship has been established, it is then possible to determine the hybridization in other C-H bonds. This treatment has been applied to many strained ring systems. Table IV lists the coupling constants and % s character for a few typical compounds. As can be seen from the table, the carbon proton bonds in cyclo-

Table IV

% s Character for Cyclic Systems

Compound	J_{C-H} c.p.s.	% s	Reference
Cyclopropane	162	32	31
Cyclobutane	136	27	31
Cyclopentane	131	26	31
Spiropentane	159	32	32
Quadricyclene	Bridge CH_2	26	28
	Bridge Head	36	28
3,3-Dimethylcyclopropene	220	44	33
IV	190	38	34

propane rings are essentially sp^2 in character. From the coupling constants the bonding in 3,3-dimethylcyclopropene should be more like acetylene than ethylene; the fact that 3,3-dimethylcyclopropene readily forms a lithium salt with n-butyl lithium is in accord with this prediction. Tricyclo-[4.1.0.0.^{2,7}]-heptane III (35) is calculated to have 40% s character in the 1 and 7 C-H bonds; the protons are sufficiently acidic to react quantitatively with n-butyl lithium.



Since J_{C-H} correlates with the state of hybridization, it might be expected that it should also correlate with such molecular properties as bond lengths, electronegativities and bond angles. Muller and Pritchard (25) proposed 7 as the form of the equation to relate the coupling constant to the carbon hydrogen bond length. Using the known values for the two types of bonds in methylacetylene as standards they obtained equation 8. The equation was then used to determine the C-H bond lengths for

$$R_{C-H} = A + BJ_{CH} \quad 7$$

$$R_{CH} = 1.1597 - 4.17 \times 10^{-4} J_{CH} \quad 8$$

several other compounds. The values obtained were in good agreement with those obtained by other methods. The same workers (25) also tried to find a relationship between J_{C-H} (and therefore hybridization) and electronegativities (E_X) of the X group in a series of methyl compounds. Some of the compounds studied are given in Table V. As

Table V

J_{C-H} and Electronegativities for Some Methyl Compounds

Compound	J_{C-H} c.p.s.	E_X
Ethane	126	2.60
Methyl amine	134	3.05
Methanol	142	3.50
Methyl fluoride	149	3.90
Methyl chloride	150	3.15
Methyl bromide	152	2.95
Methyl iodide	151	2.65

the group attached to the methyl becomes more electronegative, there should be more ionic character in the C-X bond. The hybridization in the methyl carbonium ion should be essentially sp^2 and have a coupling constant of about 167 c.p.s. For the series ethane to methyl fluoride the trend is apparent and a plot of J_{C-H} vs. E_X is linear. However the other methyl halides do not fall on this plot. The electronegativities of the halogens differ greatly but the coupling constants are very close. It will be noted that the linear relation between J_{C-H} and E_X holds if the X elements are in the same row of the periodic table. It is possible that the electronegativity effect holds for the other halogens but that some other effect, say caused by the increase in the C-X bond length or an anisotropy effect, is countering the electronegativity effect.

Since it was not possible to find a simple relationship between E_X and J_{C-H} , an equation of type 9 was tried (25). Using the known parameters for ethane, methyl fluoride and methyl iodide, equation 10 was obtained. This equation was then tested

$$J_{CH} = AE_X + BR_{C-X} + C \quad 9$$

$$J_{CH} = 22.6E_X + 40.1R_{C-X} + 5.5 \quad 10$$

on several methyl compounds. Calculated coupling constants for several X groups had a deviation of only about 2% from the experimental values. The cyano and trichloromethyl groups on the other hand showed greater deviations (about 20%). Dreeskamp and Sackmann (30) found that an equation of form 11 agreed much better with the data and gave a good fit for all groups tested. The use of either of these equations is some what limited since either E_X or R_{C-X} is needed to calculate the other.

$$J_{CH} = A + BE_X R_{C-X} \quad 11$$

Footo (23) observed that there is a correlation between the C-C-C bond angle in some hydrocarbons to the carbon hydrogen coupling constant. The cyclic alkanes from C-3 through C-10 plus norbornadiene were included in the list of hydrocarbons studied. This relation may have some potential use but appears to be very limited. All centers of compound considered were saturated. Unsaturated compounds obviously don't fit on the saturated plot. Possibly other more valuable relationships can be obtained to relate bond angles. c.f. 56.

Malinowski (36) found that an additivity relationship exists between the C^{13} proton coupling constants and the groups on the central carbon in some substituted methanes. According to his method, the coupling constant of a substituted methane

CHXYZ can be calculated from equation 12. The values of ζ_X , some of which are listed in Table VI were calculated from the coupling constants of the corresponding monosubstituted methanes. The constant ζ_H for methane is defined by equation 13. The substituent constant ζ_X for any group X is then found from 14.

$$J_{CH} = \zeta_X + \zeta_Y + \zeta_Z \quad 12$$

$$J_{CH}(\text{inHCH}_3) = 3\zeta_H \quad 13$$

$$\zeta_X = J_{CH}(\text{inCH}_3X) - 2\zeta_H \quad 14$$

Table VI

Substituent Constants for Calculation of J_{C-H}

Substituent	ζ_X c.p.s.	Substituent	ζ_X
H	41.7	F	65.6
Cl	68.6	OCH ₃	56.7
CH ₃	42.6	CN	52.6

Malinowski and co-workers (26) also developed a relationship for formyl compounds. Both methods gave good results for the compounds to which they were applied. Gutowsky and Juan (37,38) have developed a valence bond treatment to support these empirical results.

Most of the compounds treated by Malinowski contained only two X groups. Several workers (39,40,41) have found that for some trisubstituted compounds, particularly those possessing fluorine atoms, there are considerable deviations from additivity. In all cases where the large deviations were observed (see Table VIII) the calculated values were smaller than the measured quantity. Douglas (42) recognized that there seemed to be some definite additivity in the deviations. He proposed another empirical equation (equation 15) to predict all the observed coupling constants. The term $f(X)$ gives the direct effect that a group X has on the splitting. This term corresponds to $J_{CH} = N_X f(X) + N_{XY} g(X,Y) + 125$ 15 the ζ_X , ζ_Y , or ζ_Z factors of equation 12 but has a different value. N_X is the number of X groups (or Y or Z groups). The sum of the $f(X)$ terms plus 125 gives the direct or Malinowski coupling constant. The $g(X,Y)$ term represents the additional effect caused by the interactions of the fluorine, chlorine, cyano, or methoxy groups with each other. A value is added for each possible pairings of these groups. The interactions of these groups with other groups or of other groups with themselves were assumed to give zero contributions. Table VIII gives some values of coupling constants calculated by the two methods and compared

Table VII

Additivity Terms for Determination of J_{C-H} in Substituted Methanes

Direct Effect				Interaction Effect		
X	$f(X)$ c.p.s.	X	$f(X)$	X	Y	$g(X,Y)$
F	24	Cl	25	F	F	13
OCH ₃	15	CN	13	F	Cl	9
CBrF ₂	6.5	CClF ₂	6.5	F	CN	4
C(OR)F ₂	6.5	CH ₃	1	OCH ₃	OCH ₃	6
				Cl	Cl	3

Table VIII

Calculation of J_{C-H} from Equations 12 and 15

Compound	J_{C-H} obs.	J calc. eq. 12	J calc. eq. 15
CH ₃ CH ₃	126	126	126
CH ₃ CH ₂ Cl	152	153	151
CH ₂ ClCN	161	163	163
CH ₂ F ₂	185	173	186
CHF ₃	238	197	236

to the experimental values. The general use of this equation for predictions is somewhat limited since it is necessary to determine many coupling constants before an accurate prediction can be made.

An empirical method of estimating diamagnetic anisotropy effects has been developed from the correlation of proton chemical shifts to C^{13} proton coupling constants. The C^{13} proton coupling constants seem to be relatively unaffected by changes in anisotropy and solvent effects (43). The chemical shift on the other hand is much more sensitive to such changes. A series of compounds in which anisotropy and other effects are nearly constant might be expected to show a linear relation between J_{C-H} and δ_H . Some workers (27,44,45) have noted that several compounds for which anisotropy effects are predicted to be small gave a linear plot. Goldstein and Reddy (27,45) placed several compounds, for which an anisotropy effect is expected, on the same plot. They assumed that the correction necessary to bring a chemical shift onto the straight line is a measure of the anisotropy effect for the particular group. The anisotropic correction factor could then be used to correct the hydrogen chemical shift to a value that is free from the anisotropic contribution.

The C^{13} proton splitting may be conveniently employed to determine proton-proton coupling constants in cases involving equivalent protons. Trans-1,2-dichloroethene may be considered as an example. In the normal molecule V, the protons are equivalent and give only 1 peak. In VI, the a proton is split by the C^{13} and since its environment is now not the same as that for the b proton, the satellite peaks are further split, by the proton-proton coupling constant J_{HH} . Some coupling constants found by this method include: 7.5, cyclopropane (22), 9.8, acetylene (24) and 12.2, trans-1,2-dichloroethene (46,47).

Drago and Middaugh (48) have used the C^{13} proton splitting to assign the proton spectra of S-methylthioacetate. The two methyl groups have very similar chemical shifts but the C^{13} proton coupling constants for a methyl carbonyl C-H and a methyl sulfur link are quite different. Thus by assigning the satellite peaks to the proton signals, it was possible to decide which peak was caused by which methyl.

A small amount of work has been reported on nonbonded C^{13} proton couplings. For small coupling constants, the peaks may be hidden under the main signal and not be visible. Table IX gives the ranges for some of the long range coupling constants that have been reported (30,49,50). Most of these compounds were prepared for other chemical

Table IX
Long Range C^{13} Proton Couplings

Type Structure	$J_{C^{13}-C-H}$	Number of Compounds
$-C^{13} \equiv C-H$	49.5-50.8	5
$>C^{13}-CHO$	24-26.5	2
$>CH-C^{13} \equiv$	9.9-10.6	2
$>CH-C^{13}O$	5.2-6.5	11
$>C^{13}-CH<$	3.7-4.1	8

purposes and were enriched with C^{13} in a given position. In a few cases (27) the coupling between a proton and a carbon three bonds removed have been reported. The constants for 12 compounds ranged between 3.8 and 5.1 c.p.s. The long range coupling values may be of some assistance in trying to assign a structure to a carbon skeleton with relatively few protons.

Conclusion.-- C^{13} n.m.r. is already a very valuable tool in organic chemistry and should become even more useful as more workers take advantage of its potential.

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